

CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Multicenter, Observer-blinded, Noninferiority Study to Evaluate the Immunogenicity and Safety of a Quadrivalent Inactivated Influenza Virus Vaccine (Seqirus QIV) with a US-licensed Quadrivalent Inactivated Comparator Influenza Virus Vaccine (Comparator QIV) in a Pediatric Population 6 Months Through 59 Months of Age

Protocol Number:	CSLCT-QIV-15-03
Study Product:	Seqirus split-virion quadrivalent inactivated influenza virus vaccine (Seqirus QIV)
Development Phase:	3
Sponsor:	Seqirus Pty Ltd 63 Poplar Road Parkville Victoria 3052 Australia
Protocol Version:	Protocol Amendment 1_Final Version 2.0
IND Number:	IND 15974
Protocol Date:	24 MAY 2016
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Conference on Harmonisation), ethical principles that have their origin in the Declaration of Helsinki and all applicable national and local regulations.

This protocol includes information and data that contain trade secrets and privileged or confidential information that is the property of the sponsor ("Seqirus"). This information must not be made public without written permission from Seqirus. These restrictions on disclosure will apply equally to all future information supplied to you. This material may be disclosed to and used by your staff and associates as may be necessary to conduct the clinical study.

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF THE STUDY

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator Study File. This list will be updated by Seqirus (or delegate) and provided to the study sites as needed.

SIGNATURE ON BEHALF OF SPONSOR

Study Title: A Phase 3, Randomized, Multicenter, Observer-blinded, Noninferiority Study to Evaluate the Immunogenicity and Safety of a Quadrivalent Inactivated Influenza Virus Vaccine (Seqirus QIV) with a US-licensed Quadrivalent Inactivated Comparator Influenza Virus Vaccine (Comparator QIV) in a Pediatric Population 6 Months Through 59 Months of Age

Protocol Number: CSLCT-QIV-15-03

I have read the protocol entitled "*A Phase 3, Randomized, Multicenter, Observer-blinded, Noninferiority Study to Evaluate the Immunogenicity and Safety of a Quadrivalent Inactivated Influenza Virus Vaccine (Seqirus QIV) with a US-licensed Quadrivalent Inactivated Comparator Influenza Virus Vaccine (Comparator QIV) in a Pediatric Population 6 Months Through 59 Months of Age*" and confirm that, to the best of my knowledge; the protocol accurately describes the design and conduct of the study.

[Redacted Signature Area]

[Redacted Signature Area]

Date

SIGNATURE OF INVESTIGATOR

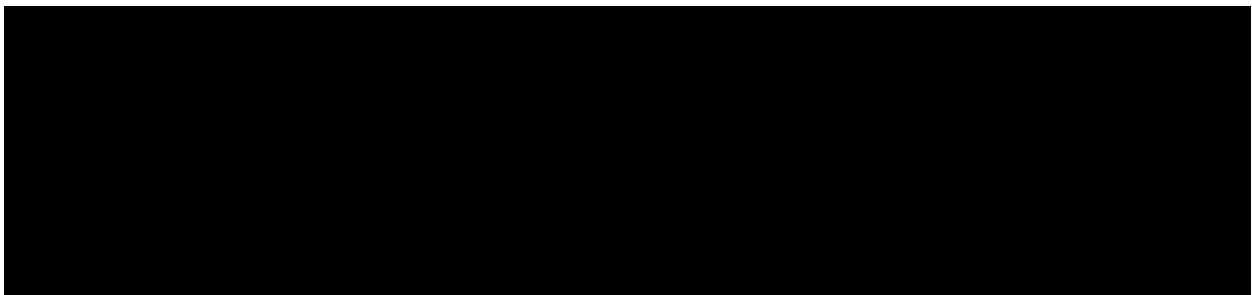
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By signing this protocol, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki, the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation) and applicable regulatory requirements.

Changes to the protocol will only be implemented after written approval is received from (Seqirus Pty Ltd, ‘Seqirus’) and the Institutional Review Board or Independent Ethics Committee (as appropriate), with the exception of medical emergencies.
I will ensure that study staff fully understand and follow the protocol.



PROTOCOL SYNOPSIS

Title	A Phase 3, Randomized, Multicenter, Observer-blinded, Noninferiority Study to Evaluate the Immunogenicity and Safety of a Quadrivalent Inactivated Influenza Virus Vaccine (Seqirus QIV) with a US-licensed Quadrivalent Inactivated Comparator Influenza Virus Vaccine (Comparator QIV) in a Pediatric Population 6 Months through 59 Months of Age
Protocol Number	CSLCT-QIV-15-03
Sponsor	Seqirus Pty Ltd (Seqirus) 63 Poplar Road, Parkville, Victoria 3052 Australia
Development Phase	3
Study Product	Seqirus split-virion quadrivalent inactivated influenza virus vaccine (Seqirus QIV)
Indication	Prophylaxis of influenza
Study Summary	<p>Influenza is a highly infectious disease caused by the influenza virus, an orthomyxovirus with two clinically relevant types (types A and B). The disease is characterized by the abrupt onset of respiratory and systemic symptoms, such as fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis, and occurs in epidemics throughout the northern and southern hemisphere winter months in temperate climates. During influenza epidemics, there is increased mortality among older adults (age > 65 years), people with chronic diseases, and very young children (age 0 to 12 months), as well as an increase in morbidity and hospitalization because of influenza-associated complications. Influenza epidemics have been associated with the circulation of single or multiple strains from either one of the two A subtype viruses (H3N2 or H1N1), or type B viruses.</p> <p>Influenza type B viruses show extensive variation in antigenicity. Although only one subtype is known to exist, influenza type B viruses have separated into two distinct genetic lineages since 1985, Yamagata and Victoria. B strains from either lineage may circulate and cause infection, and mismatch may occur between circulating B strains and influenza vaccine B strains due to antigenic variation over time. On average, influenza B strain accounts for approximately 25% of positive specimens in the US. The burden of infection is largely school age children, young adults and older adults, however, young children experience the highest</p>

mortality. Mismatches between the B strain in the vaccine and the circulating strain occur in approximately 5 out of every 10 influenza seasons.

Recently, a number of quadrivalent inactivated influenza vaccines have been licensed in the US, containing representative vaccine strains for the H1N1 and H3N2 A subtypes and both B-strain lineages. These vaccines may improve overall vaccine effectiveness by reducing the impact that B strain vaccine mismatch can make on total influenza morbidity and mortality. The Centers for Disease Control and Prevention have estimated that in a season where there is a B strain mismatch, availability of quadrivalent influenza virus vaccines could prevent 1 million cases, 7000 hospitalizations and 320 deaths in the USA.

The Seqirus split-virion quadrivalent inactivated influenza virus vaccine (Seqirus QIV) used in this study for subjects 36 months through 59 months of age is formulated to contain 15 micrograms (mcg) of hemagglutinin (HA) per 0.5mL dose for each included influenza virus strain, including representative strains of both B lineages. This QIV formulation is consistent with the currently-licensed Afluria trivalent influenza virus vaccine, except that it contains an additional B influenza strain so that the total HA concentration is 120 mcg HA/mL, from four strains.

The pediatric dose of QIV used in this study for subjects 6 months through 35 months of age is formulated to contain 7.5 mcg of HA per 0.25mL dose for each included influenza virus strain, including representative strains of both B lineages

This phase 3 study is a randomized, observer-blinded, comparator controlled study of Seqirus QIV versus a US-licensed 2016-2017 comparator QIV containing the same influenza strains recommended in the United States for the 2016-2017 season.

Primary Objective(s)	To demonstrate that vaccination with Seqirus QIV elicits an immune response that is not inferior to the US-licensed comparator QIV (Comparator QIV) containing the same virus strains as Seqirus QIV among a pediatric population 6 months through 59 months of age.
Primary Endpoint(s)	The immunogenicity of study vaccines will be assessed at least 28 days after the last vaccine administration by measuring the hemagglutination inhibition (HI) antibody titers to the 4 viral

strains included in the vaccines.

The noninferiority of Seqirus QIV compared to US licensed comparator QIV will be assessed by the 8 co-primary endpoints of geometric mean titer (GMT) and seroconversion rate (SCR) for each viral strain contained in the vaccines as follows:

- The GMT ratio* for the A/H1N1 strain;
- The GMT ratio for the A/H3N2 strain;
- The GMT ratio for the B strain (Yamagata lineage);
- The GMT ratio for the B strain (Victoria lineage);

- The difference between the seroconversion rates** for the A/H1N1 strain;
- The difference between the seroconversion rates for the A/H3N2 strain;
- The difference between the seroconversion rates for the B strain (Yamagata lineage);
- The difference between the seroconversion rates for the B strain (Victoria lineage).

**The GMT ratio is defined as the geometric mean of postvaccination (Study Exit Visit) HI titer for the US licensed comparator QIV over the geometric mean of postvaccination (Study Exit Visit) HI titer for Seqirus QIV.*

***The rate of seroconversion is defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer \geq 1:40 or a prevaccination HI titer \geq 1:10 and a \geq 4-fold increase in postvaccination HI titer.*

Secondary Objective(s)

The secondary objectives of the study are:

1. To assess the safety and tolerability of Seqirus QIV in two age strata: 6 months through 35 months, and 36 months through 59 months, as well as overall.

2. To characterize the immunogenicity of Seqirus QIV and the US-licensed comparator QIV in two age strata: 6 months through 35 months, and 36 months through 59 months, as well as overall.

Secondary Endpoint(s)

Secondary Endpoints:

Secondary Safety Endpoints:

- Frequency and severity of solicited local reactions and systemic adverse events (AEs) for 7 days after each

- vaccination dose;
- Frequency of cellulitis-like reactions for at least 28 days after each vaccination dose;
- Frequency and severity of unsolicited AEs for at least 28 days after each vaccination dose;
- Frequency of serious adverse events (SAEs) for at least 180 days after the last vaccination dose.

Secondary Immunogenicity Endpoints:

The humoral immune response will be assessed in terms of HI antibodies for both the Seqirus QIV and Comparator QIV. Serum HI antibody titers against the 4 influenza vaccine strains will be used to calculate:

- Geometric mean titer (GMT): Geometric mean of HI titers prevaccination (Day 1) and postvaccination (Study Exit Visit);
- Seroconversion rate: Percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer \geq 1:40 or a prevaccination titer \geq 1:10 and a \geq 4-fold increase in postvaccination titer;
- The percentage of subjects with a titer \geq 40 (seroprotection rates) at Day 1 and Study Exit Visit;
- Geometric Mean Fold increase (GMFI)^{***}: Geometric mean-fold-titer rise from Day 1 to Study Exit Visit.

****The rate of seroprotection is defined as the proportion of subjects with an HI titer \geq 1:40.*

*****GMFI in antibody titer is defined as the geometric mean of the fold increase of postvaccination HI antibody titer over the prevaccination HI antibody titer.*

Exploratory Objective	To assess the frequency of antipyretic use in the first 7 days postvaccination in two age strata: 6 months through to 35 months, and 36 months through 59 months, as well as overall according to treatment group.
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Exploratory Endpoint	Frequency of antipyretic use in the first 7 days after each vaccination dose.
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Study Design	This study is a randomized, observer-blinded, comparator controlled study of Seqirus QIV, administered intramuscularly versus a US licensed comparator QIV containing the same influenza strains recommended by the US Food and Drug
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Administration (FDA) and Vaccines and Related Biological Products Advisory Committee (VRBPAC) for the 2016-2017 season. The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle of the arm if muscle mass is adequate) in children 12 months through 35 months of age, or the deltoid muscle of the non-dominant arm in children 36 months through 59 months of age. The study will be conducted during the 2016-2017 Northern Hemisphere influenza immunization season in male and female subjects 6 months through 59 months of age.

After parent(s)/guardian(s) have provided written informed consent (Visit 1 [Day 1]), eligible subjects will be stratified by age to one of two age cohorts:

- Cohort A comprising subjects 6 months through 35 months of age;
- Cohort B comprising subjects 36 months through 59 months of age.

The Interactive Response Technology (IRT) will include a quota for each age stratum so that no more than 60% of the total sample size is represented in each age stratum.

A step-down approach to enrollment is designed to allow the opportunity to assess safety data prior to enrolling the younger cohort ie, 6 months through 35 months of age.

Subjects in the 36 through 59 months age cohort will be enrolled and randomized first until approximately one third of subjects (or a minimum of 300 subjects) in this age cohort have received the first vaccination and have had an opportunity to enter at least 7 days of safety data postvaccination. A safety data cut will then be performed and a Data and Safety Monitoring Board (DSMB) meeting convened to review and assess the available safety data.

Recruitment in the 36 through 59 months age cohort will not be halted during the period of the data cut and DSMB review. Enrollment in the younger age cohort (subjects 6 months through 35 months of age) will only commence after the DSMB has reviewed the safety data and recommended that the study may proceed.

A second safety data cut will be performed when approximately one third of subjects (or a minimum of 300 subjects) in the 6

through to 35 months age cohort have received the first vaccination and have had an opportunity to enter at least the 7 days of safety data postvaccination, A DSMB meeting will be convened to review and assess the available safety data. Recruitment in the 6 through 35 months age cohort will not be halted during the period of the data cut and DSMB review.

After stratification, subjects will be randomized to one of the two treatment groups using a 3:1 allocation ratio to receive either Seqirus QIV or the US licensed comparator QIV.

Subjects will provide pre- and postvaccination serological specimens as well as structured safety follow-up.

Screening evaluations will be performed either the day of the vaccination or within a maximum of 1 week before vaccination and include medical history, and targeted physical examination (if clinically indicated). Vaccination will occur on Day 1. On Day 1 and prior to vaccination, a serum sample will be collected for influenza-specific serology.

The parent(s)/guardian(s) of subjects will record electronically:

1. In a “7-Day Diary”: the occurrence of solicited AEs, a pre-specified series of local reactions and systemic symptoms and temperature that may occur between Day 1 and Day 7 after a vaccination.
2. In an “Other Body Symptoms Diary”, any unsolicited AEs that may occur between Day 1 and the Study Exit Visit.
3. In a “Medication Diary”, all concomitant medication use that may occur between Day 1 and the Study Exit Visit.

Subjects will return to the clinic 28 (+4) days after each indicated vaccine dose. During this visit, entries in the 7-Day Diary, the Other Body Symptoms Diary and the Medication Diary will be reviewed with the parent(s)/guardian(s) and a targeted physical examination performed as clinically indicated. For one-dose schedule subjects, Visit 2 (Day 29+4) postvaccination is the Exit Visit. For two-dose schedule subjects, Visit 3 (Day 29+4 post-second vaccination) is the Exit Visit. SAEs and adverse events of special interest (AESIs) will be collected via a telephone call at least 90 days after the last vaccination dose (Day 90+7) and another at 180 days after the last vaccination dose (Day 180+7).

Analyses of safety data may be triggered by the DSMB if halting rule criteria are met in either study age cohort, or following ad-hoc requests for review by Seqirus as described in the DSMB Charter.

An interim analysis will be made once all subjects have completed all immunogenicity assessments and all solicited and unsolicited adverse event reporting, and results will be presented in an interim study report. A final clinical study report will present all immunogenicity and safety data collected from the active study period and safety data through to the final evaluation (180 days following the last vaccination dose).

Number of Subjects

Approximately 1500 subjects will be enrolled into the Seqirus QIV group and 500 in the Comparator QIV group. This provides a total of 2000 evaluable subjects, assuming a 10% dropout rate. Thus a total of 2222 will be enrolled for the study. The subjects will be unequally balanced between the Seqirus QIV and Comparator QIV group.

Study Duration

Subjects will receive one or two doses of Study Vaccine depending on their age at the time of administration of the first dose of Study Vaccine and previous vaccination status. The follow-up period will be 180 days from the last vaccination. The maximum study duration for an individual subject receiving a single vaccination will be up to 7 months (up to 7 days screening period, 28+4 days active study period and 180+7 days safety follow-up period).

The maximum study duration for an individual subject scheduled for the two-vaccination regimen will be up to 8 months (up to 7 days screening period, 28+4 days active study period after each Study Vaccine dose, and 180+7 days safety follow-up period after the last vaccination dose).

The overall study duration (ie, first subject's screening visit to last subject's end-of-study visit) will be a maximum of 10 months.

Study Population and Main Criteria for Eligibility

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to participate in this study:

1. Male or female subject 6 months through to 59 months of age at the time of first vaccination and born between 36 and 42 weeks of gestation;
2. Parent or legally acceptable representative able to provide written informed consent and be willing and able to adhere to all protocol requirements including blood draws.
3. Subject is in generally good health as per the Investigator's medical judgment.

Exclusion Criteria:

If one or more of the following exclusion criteria are met, the subject will be ineligible to take part in this study:

1. History of allergic reactions to egg proteins or any components of the Study Vaccines;
2. History of serious adverse reactions to any influenza vaccines;
3. History of Guillain-Barré syndrome or other demyelinating disease such as encephalomyelitis and transverse myelitis;
4. History of licensed or investigational influenza vaccination in the last 6 months;
5. Clinical signs of active infection and/or an axillary temperature of $\geq 99.5^{\circ}\text{F}$ / ($\geq 37.5^{\circ}\text{C}$) on the day of vaccination or within 48 hours preceding vaccination. Study entry may be deferred for such individuals, at the discretion of the Investigator;
6. Current or recent, acute or chronic medical conditions that in the opinion of the Investigator are clinically significant and/or unstable (such as illness exacerbations) which within the preceding 30 days:
 - a) required hospitalization; or
 - b) associated with significant organ function deterioration;or
 - c) associated with major changes to treatment dosages due to disease instability* ; or
 - d) required major new treatments.

** recent changes to treatments not related to disease instability, such as routine summer dose reductions to agents for attention deficit hyperactivity disorder (ADHD) are permitted.*
7. History of any seizures, with the exception of a single febrile seizure;
8. Self-reported or known seropositivity suggestive of acute or chronic viral infection for human immunodeficiency virus, hepatitis B or hepatitis C;
9. Known or suspected congenital or acquired immunosuppressive conditions;
10. Current or recent immunosuppressive or immunomodulatory therapy, as follows:
 - a) Chronic (> 2 weeks) or long-term systemic corticosteroids: ≥ 0.125 mg/kg/day of oral prednisolone or equivalent daily;
 - b) Sporadic systemic corticosteroids: ≥ 0.5 mg/kg/day of oral prednisolone or equivalent for two or more short courses of > 3 days in the 3 months preceding vaccination;

Note: Use of topical or inhalant corticosteroids prior to administration of the Study Vaccine or throughout the study is

acceptable.

11. Current or medical history of malignant neoplasms;
12. Administration of immunoglobulin and/or any blood products within the previous 90 days preceding the administration of the Study Vaccine or planned administration during the study;
13. Participation in a clinical trial or use of an investigational compound (ie, a new chemical or biological entity not registered for clinical use, including investigational vaccines) within 28 days prior to or 28 days after receiving the Study Vaccine, or plans to enter a study during this period;
14. Vaccination with a licensed vaccine 21 days (for live or inactivated vaccines) prior to receiving the Study Vaccine, or plans to receive any licensed vaccine prior to the Study Exit Visit;
15. Medical conditions or treatments contraindicating intramuscular vaccination due to increased risk of bleeding. These may include known bleeding disorders (such as thrombocytopenia), or treatment with anticoagulants (such as warfarin) in the 3 weeks preceding vaccination. However, antiplatelet agents such as low-dose aspirin, ticlopidine (Ticlid) and clopidogrel (Plavix) are permitted;
16. Family members of the employees of the Investigator or study center with direct involvement in the study, or with other clinical studies under the direction of that Investigator or study center.

**Study Product Dose,
Dosing Regimen and
Administration**

Seqirus QIV (Seqirus quadrivalent, split-virion inactivated influenza vaccine), administered as an intramuscular dose into the deltoid muscle or anterolateral aspect of the thigh.

Subjects will receive either one or two doses of Study Vaccine depending on their previous history of influenza virus vaccination.

Subjects 6 months through 35 months of age will receive one or two 0.25 mL doses according to the current US Advisory Committee on Immunization Practices (ACIP) dosing recommendations. Each 0.25 mL dose contains 7.5 mcg hemagglutinin antigen from each of the following four influenza strains: A (H1N1)-like virus; A (H3N2)-like virus; B (Yamagata lineage) and B (Victoria lineage) recommended by the FDA VRBPAC for the 2016-2017 influenza season in the US.

Subjects 36 months through 59 months of age will receive one or two 0.5 mL doses according to the current ACIP dosing recommendations. Each 0.5 mL dose contains 15 mcg hemagglutinin antigen from each of the following four influenza

strains: A (H1N1)-like virus; A (H3N2)-like virus; B (Yamagata lineage) and B (Victoria lineage) recommended by the FDA VRBPAC for the 2016-2017 influenza season in the US.

Comparator Product, Dose, Dosing Regimen and Administration

The US-licensed comparator QIV is an inactivated influenza vaccine, administered and presented according to the licensed prescribing information for the vaccine.

Each dose should contain 7.5 or 15 mcg hemagglutinin antigen from each of the four influenza strains recommended by the FDA VRBPAC for the 2016-2017 influenza season in the US.

The comparator vaccine dosage regimen is also administered in accordance with the 2016-2017 influenza vaccination dose recommendations as for the study product dose above.

Study Procedures

Recruitment

Subjects will be recruited through generic advertisements or Institutional Review Board (IRB)-approved study-specific advertisements. For those potential subjects interested in participating in the study, an appointment will be scheduled to allow informed consent to be obtained. Written informed consent can be provided by subjects up to 1 week prior to the day of vaccination. The subject's influenza vaccination history will determine the dosing regimen (a single vaccination or a two-vaccination regimen administered 28 days apart). The first vaccination will be administered at Visit 1 (Day 1) and the second vaccination, if scheduled, will be administered at Visit 2 (Day 29+4).

Visit 1 (Day 1) – Day of Vaccination (Either 1 or 2 Dose Schedule)

Informed Consent:

The parent(s)/guardian(s) of subjects must provide written informed consent prior to any study-related procedures. Subjects with parent(s)/guardian(s) informed consent will be issued a unique, subject number, including those who prove to be screen failures.

Prevaccination:

The following assessments will be performed and documented in the source notes:

- A review of the subject's medical history, including concomitant medications, vaccination history (including
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- influenza vaccination) and documentation of any relevant medical history;
- Targeted physical examination as clinically indicated following the collection of medical history;
 - Subject's axillary temperature and body weight;
 - A review of the subject's eligibility according to the Inclusion/Exclusion criteria
 - Collection of at least 3 mL blood sample.

Subjects who complete the above assessments and who fulfill the inclusion/exclusion criteria will be eligible for randomization. Eligible subjects will be assigned the next available, unique subject number and corresponding Study Vaccine.

Vaccination:

As per the US ACIP guidelines for seasonal influenza vaccination, the subject's age and influenza vaccination history determines the dose and dosing regimen (a single vaccination or a two-vaccination regimen administered 28 days apart). The first vaccination will be administered at Visit 1 (Day 1) and the second vaccination, if scheduled, will be administered at Visit 2 (Day 29 + 4). The Investigator/delegate will administer the study vaccine according to the randomization code into the deltoid region of the arm or into the anterolateral aspect of the thigh, by intramuscular injection. Where possible, the injection will be administered into the contralateral arm to which the blood sample was drawn.

Subjects will receive the following dose depending upon their age at the time of administration of the first dose of Study Vaccine:

- Cohort A** 6 months through 35 months of age 0.25 mL;
Cohort B 36 months through 59 months of age 0.5 mL.

Postvaccination:

- Subjects will be observed for at least 30 minutes postvaccination for the signs of an anaphylactic reaction. Appropriate medical treatment will be readily available in case of emergency.
- Parent(s)/guardian(s) will be issued with a digital thermometer and Local Reaction Measurement Card, and provided with electronic access to the 7-Day Diary (for recording solicited AEs), the Other Body Symptoms Diary (for recording unsolicited AEs), and the Medication Diary (for recording new concomitant medications). The 7-Day Diary

will be completed on the day of vaccination and for the subsequent 6 days following vaccination (total of 7 days). The Other Body Symptoms Diary and the Medication Diary will be completed on the day of vaccination until the next study visit.

- Parent(s)/guardian(s) will be reminded on how to measure axillary temperature and record their child's temperature at the same time each evening, in addition to completing the diaries.
- Parent(s)/guardian(s) will be instructed to contact the Investigator/delegate immediately if the subject experiences any signs or symptoms with grade 3 intensity.
- Parent(s)/guardian(s) will be educated on how to recognize the signs/symptoms of an influenza-like illness (ILI) and will be instructed to contact the investigator/delegate immediately if the subject experiences any signs or symptoms of an ILI from Day 1 until the Study Exit Visit.
- An appointment will be made for each subject to return to the clinic 28 + 4 days after Visit 1.

Diary Reminder Telephone Call (Day 3 + 2):

Sites will contact parent(s)/guardian(s) of subjects by telephone between Days 3 and 5 inclusive, to check that the electronic diaries are being completed daily, and to address any questions on how to complete them correctly.

Visit 2, Study Exit Visit (Single Dose Schedule) Day 29 + 4

Subjects who are scheduled to receive a single dose of study vaccine according to the previous immunization history, will exit the study at this visit.

The following will be undertaken and recorded at the Exit Visit:

- Review of the electronic diary entries;
- Assessment of the occurrence of any SAEs and AESI;
- Targeted physical examination as clinically indicated;
- Collection of at least 3 mL blood sample.

OR

Visit 2, Second Vaccination (Two-Dose Schedule) Day 29 + 4

Subjects who are scheduled to receive 2 doses of study vaccine will require a second dose of study vaccine at this visit.

Prevaccination:

The following will be undertaken and recorded prior to administration of the second dose of study vaccine:

- Review of the electronic diary entries;
- Assessment of the occurrence of any AEs, SAEs and AESIs;
- Subject's ongoing eligibility will be reviewed;
- Targeted physical examination as clinically indicated;
- Subject's axillary temperature.

Vaccination:

Subjects will be injected according to the same procedure as for the first dose.

Subjects who are scheduled to receive 2 doses of study vaccine and who turn 36 months of age between the two study vaccinations will receive a second dose of 0.25 mL of study vaccine.

Postvaccination:

- Subjects will be observed for at least 30 minutes after vaccination for the signs of an anaphylactic reaction;
- Parent(s)/guardian(s) will be reminded to complete the 7-Day Diary entries for the day of the second vaccination and for the subsequent 6 days following vaccination (total of 7 days), and to continue recording unsolicited AEs in the Other Body Symptoms Diary and concomitant medications in the Medications Diary from the day of the second vaccination until the Study Exit Visit;
- Parent(s)/guardian(s) will be reminded on how to measure axillary temperature and record their child's temperature at the same time each evening, in addition to completing the diaries;
- Parent(s)/guardian(s) will be instructed to contact the Investigator/delegate immediately if the subject experiences any signs or symptoms with grade 3 intensity;
- Parent(s)/guardian(s) will be reminded on how to recognize the signs/symptoms of an ILI and will be instructed to contact the investigator/delegate immediately if the subject

experiences any signs or symptoms of an ILI from Visit 2 until the Study Exit Visit;

- An appointment will be made for each subject to return 28 + 4 days post-Dose 2 for a Study Exit Visit.

Diary Reminder Telephone Call (Day 3 + 2 after the second vaccination):

Sites will contact parent(s)/guardian(s) of subjects by telephone between Days 3 and 5 inclusive after the second vaccination, to check that the diaries are being completed daily, and to address any questions on how to complete them correctly.

Visit 3, Study Exit Visit (Two-dose Schedule)

The Study Exit Visit for the Two-dose Schedule will occur 28 + 4 days after the administration of the second dose of Study Vaccine (Visit 2).

The following will be undertaken and recorded at this study visit:

- Review of the electronic diary entries;
- Assessment of the occurrence of any AEs, SAEs and AESIs;
- Targeted physical examination as clinically indicated;
- Collection of at least 3 mL blood sample.

Postvaccination Safety Follow-up Telephone Call (Day 90+7 and 180+7 after Last Vaccination)

Serious adverse event and AESI information will be collected for a total of 180 days (180+7 days) after administration of the last dose of study vaccine:

Unscheduled Visit - Influenza-like Illness (ILI) Visit

Subjects reporting signs/symptoms of an ILI between Visit 1 and Study Exit Visit (Visit 2 or Visit 3) will be asked to attend an additional clinic visit within 72 hours of the symptoms meeting the case definition of an ILI, for confirmation of the ILI.

The criteria for an ILI are as follows:

- Elevated axillary temperature of $\geq 99.5^{\circ}\text{F}$ ($\geq 37.5^{\circ}\text{C}$) or a clear history of fever or chills); and

- At least one respiratory symptom: including sore throat, cough, wheezing, rhinorrhea/rhinitis; and
- At least one systemic symptom, including myalgia, headache, malaise and fatigue, nausea and/or vomiting, diarrhea, loss of appetite and irritability.

Upon confirmation that the ILI case definition is met, the subject's temperature will be assessed and attempts will be made to diagnose influenza viral infection by obtaining nasal and throat swab specimens. These will be analyzed for laboratory confirmation of influenza A and/ or B by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR).

Unscheduled Visit – Cellulitis-like Reaction

Subjects reporting signs/symptoms of a Cellulitis-like Reaction between Day 1 and Study Exit Visit will be asked to attend an additional clinic visit within 24 hours (up to 3 days if on a weekend) of the symptoms meeting the definition of a Cellulitis-like Reaction.

The criteria for a Cellulitis-like Reaction are concurrent presence of all three of the following:

- Grade 3 injection site pain;
- Grade 3 injection site erythema;
- Grade 3 injection site induration.

Investigational site staff will assess for the presence of ulceration, abscess, or necrosis at the injection site.

Efficacy Assessments

Efficacy assessment involves the assessment of immunogenicity on the basis of HI antibody titer to each strain. Immunogenicity will be expressed as:

- *HI antibody titer for each strain.* All analyses involving HI antibody titer (namely GMT within a treatment group) will be based on the log scale and the resultant summary statistic back-transformed to derived GMT;
 - *Seroconversion.* For each strain the subjects will be classified as 'seroconverted' if either they have a prevaccination HI antibody titer < 1:10 and a postvaccination HI antibody titer \geq
-

1:40 or a prevaccination HI antibody titer \geq 1:10 and a \geq 4-fold increase in postvaccination HI antibody titer. Otherwise they will be classified as ‘not seroconverted’;

- *Seroprotection*. For each strain a subject will be classified as ‘seroprotected’ if their HI antibody titer \geq 1:40 at Days 1 and the Study Exit Visit. If they do not have both antibody titers \geq 1:40 they will be classified as ‘not seroprotected’;
- *Fold increase*. For each strain the fold increase for each subject will be calculated by taking the ratio of the postvaccination antibody titer over the prevaccination antibody titer;

Covariate adjusted analyses will be performed as outlined in the Statistical Analysis Plan (SAP).

Immunogenicity Analyses (Day 1 and Study Exit Visit):

Immunogenicity analyses in terms of HI antibody titers specific for the virus strains included in the vaccines will be performed on serum specimens taken at Day 1 (Visit 1) and at the Study Exit Visit (Visit 2 – single dose schedule or Visit 3 – two-dose schedule).

Safety Assessments

Safety will be assessed through solicited local reactions, solicited systemic AEs, unsolicited AEs, and SAEs.

Type, frequency and intensity of solicited local reactions through Day 7 (Day 1, 2, 3, 4, 5, 6, 7) following each study vaccination dose. These include pain, erythema/redness, and induration/swelling.

Frequency of cellulitis-like reaction for 28 days following each vaccination. Cellulitis-like reaction is defined as the concurrent presence of grade 3 injection site pain, erythema/redness and induration/swelling.

Type, frequency, duration and intensity of solicited systemic AEs through to Day 7 (Day 1, 2, 3, 4, 5, 6, 7) following each study vaccination dose. These include headache, malaise and fatigue, myalgia, fever, diarrhea, and nausea and/or vomiting for children 36 months through 59 months of age, and fever, diarrhea, nausea and/or vomiting, loss of appetite, and irritability for children 6 months through 35 months of age.

Frequency of antipyretic use in the 7 days after each vaccination dose

Type, frequency, duration and intensity of unsolicited AEs for at least 28 days following each study vaccination dose.

	Frequency of SAEs and AESIs for at least 180 days following the last vaccination dose.
Pharmacokinetics	Not Applicable.
Pharmacodynamics	Not Applicable.
Other Assessments	Not Applicable.
Statistical Analyses	<p>Primary Immunogenicity Analysis</p> <p>The primary objective is to demonstrate that vaccination with Seqirus QIV elicits a noninferior immune response compared to a US licensed comparator QIV among a pediatric population 6 months through 59 months of age.</p> <p>Co-primary immunogenicity endpoints of geometric mean titer (GMT) and seroconversion rate for each virus strain contained in the vaccine will be assessed. The rate of seroconversion is defined as the percentage of subjects with either a prevaccination hemagglutinin inhibition (HI) titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination titer.</p> <p>The noninferiority of Seqirus QIV compared to the US licensed comparator QIV will be assessed by the 8 co-primary endpoints of GMT and seroconversion rate.</p> <p>In line with the FDA Guidance on seasonal inactivated influenza vaccines (<i>Guidance for Industry Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines 2007</i>) Seqirus QIV will be considered to be noninferior to the US licensed comparator QIV for each strain if:</p> <ul style="list-style-type: none"> • The upper bound of the two-sided 95% confidence interval (CI) on the ratio of the GMTs does not exceed 1.5. The GMT ratio will be calculated by $\text{GMT}_{\text{Comparator QIV}} / \text{GMT}_{\text{Seqirus QIV}}$ • The upper bound of the two-sided 95% CI on the difference between the seroconversion rates does not exceed 10%. The difference in seroconversion rate will be calculated by $(\text{Seroconversion}_{\text{Comparator QIV}} - \text{Seroconversion}_{\text{Seqirus QIV}})$. <p>To determine the GMT ratio (adjusted analysis) a general linear</p>

model (GLM) will be fitted on log transformed postvaccination HI titer (titer) as the outcome variable and with inclusion of covariates such as vaccine treatment, prevaccination HI titer, age stratum, sex, vaccination history, age-by-vaccine interaction and study site.

From the model an adjusted difference in least square means (on the log scale) will be produced with 95% confidence limits. The estimated difference and the confidence limits will be back transformed to obtain an *adjusted GMT ratio* with 95% confidence limits. Each of the four strains will be analyzed separately. The adjusted GMT ratio will be the result for which the noninferiority assessment will be based on. The measure of the *unadjusted* GMT ratio based on postvaccination GMTs only will also be presented.

Secondary Objectives:

Secondary objectives include assessing the safety and tolerability of Seqirus QIV in two age strata: 6 months through 35 months and 36 months through 59 months of age, as well as overall.

The proportion of subjects with AEs in the two treatment arms will be presented. Adverse events will be monitored postvaccination as per the following:

1. Solicited local adverse reactions and systemic AEs through Day 7 (Days 1, 2, 3, 4, 5, 6, 7) after each vaccination dose;
2. Cellulitis-like reaction and cellulitis for 28 days after each vaccination dose;
3. Unsolicited AEs for at least 28 days following each vaccination dose;
4. Serious adverse events (SAEs) for at least 180 days following the last vaccination dose.

The frequency, duration and intensity of solicited and unsolicited AEs will be summarized for each age group and study vaccine. The proportion of subjects reporting each type of AE will be presented along with percentages and confidence intervals. Solicited local adverse reactions and systemic AEs will be summarized by frequency, duration and intensity. Unsolicited AEs will be summarized by body system and intensity. If sufficient numbers of cases of AEs occur, more formal statistical analyses of event rates or intensity may be conducted.

Further details of planned analyses will be specified in the Statistical Analysis Plan (SAP).

Statistical Considerations for Sample Size Calculations:

Seqirus QIV will be tested against a US licensed comparator QIV. The treatment randomization ratio is 3:1 (Seqirus QIV: Comparator QIV). This study is designed to achieve at least 80% power to demonstrate noninferiority for all of the 8 co-primary endpoints, seroconversion rates for 4 strains, GMT for 4 strains using a one-sided alpha of 0.025 for each comparison. No adjustment for multiple endpoints was made. For comparisons of SCR a noninferiority margin of 10% (Seqirus QIV - Comparator QIV) will be employed. It is assumed that the SCR for all strains for QIV is 50% and that there is no difference between Seqirus QIV and Comparator QIV.

For comparison of GMT ratio a noninferiority margin of 1.5 (Comparator QIV/ Seqirus QIV, equivalent to a difference on the log scale of 0.405465108) will be employed. It is assumed that there is no difference between Seqirus QIV and Comparator QIV (ie, a ratio of 1, difference on the log scale of 0) and that the standard deviation of log (titer) is 1.4.

Under these assumptions and with n evaluable = 1500 in the Seqirus QIV group and 500 in the Comparator QIV the power for 4 GMT ratio endpoints is 99.95% and the power for 4 SCR endpoints is 89.70%. The overall global power of the 8 endpoints is then $89.7\% \times 99.95\% = 89.66\%$. This provides a total N evaluable = 2000 (with 10% dropouts N=2222). Sample size calculations were performed using SAS v9.3.

Interim Analyses

An interim analysis will be made once all subjects have completed all immunogenicity assessments and all solicited and unsolicited adverse event reporting.

Enrollment Halting Rules

Enrollment into the study and study vaccination will be halted for DSMB review/ recommendation for continuation if during the 7 days after vaccination (Day 1 to Day 7) any of the following occur:

- One or more subject experiences an AE that is serious, unexpected, and is assessed as related to Study Vaccine;
- One or more subject experiences an AE that is life-threatening or causes death;
- One or more subject experiences a serious febrile AE, defined as any AE meeting seriousness criteria that is also associated with a fever of $\geq 101.3^{\circ}\text{F}$ / $\geq 38.5^{\circ}\text{C}$ (axillary);
- One or more of the subjects experiences a severe (grade 3)

- allergic reaction (eg, hives, angioedema, allergic asthma, systemic anaphylaxis);
- Vaccine-related injection site ulceration, abscess, or necrosis;

Additionally, enrollment into the study and study vaccination will be halted pending review by the DSMB if during Day 1 to Day 7, the following defined halting rule criteria are met in either study cohort (6 months through 35 months or 36 months through 59 months):

- $\geq 5\%$ of subjects enrolled to date with concurrent grade 3 pain, erythema, and induration (a cellulitis-like reaction) that is assessed as related to Study Vaccine.
(Note: If the total number of subjects enrolled to date is less than 60, a minimum of 3 subjects experiencing a concurrent severe vaccine-associated pain, erythema or induration will be needed to halt further enrollment);
- $\geq 5\%$ of subjects enrolled to date, experience a fever of $\geq 101.3^{\circ}\text{F}$ [$\geq 38.5^{\circ}\text{C}$] (axillary) that is assessed as related to Study Vaccine.
(Note: if the total number of subjects enrolled to date is less than 60, a minimum of 3 subjects is required to trigger the halt).

In addition, the DSMB chair will be immediately notified of any SAE, regardless of causality or expectedness assessment, occurring during Day 1 to Day 7. The DSMB chair will then make a determination regarding the necessity of a DSMB meeting and/or study halt in response to these events.

Data Safety Monitoring Board

An independent DSMB will monitor subject safety during the study. The DSMB will comprise clinical study experts with experience in vaccine studies and safety assessment. The DSMB will provide recommendations for stopping or continuing the study based on the assessment of study safety data according to processes defined in the study protocol and the DSMB Charter.

Schedule of Assessments – Single Dose Regimen

Assessment		Visit 1	Phone call	Visit 2	Phone call	Phone call
	Pre-Study	Vaccination	Diaries Reminder	Exit Visit	SAE Follow-up	SAE Follow-up
	Day -7 to -1	Day 1	Day 3 + 2	Day 29 + 4	Day 90 + 7	Day 180 + 7
Invitation to participate		✓ ¹				
Informed consent		✓ ¹				
Demographics and influenza vaccination history		✓ ¹				
Medical history and baseline medication use		✓ ¹				
Targeted physical examination (<i>if necessary</i>)		✓ ¹		✓		
Body weight		✓ ¹				
Axillary temperature		✓				
Review of eligibility criteria		✓				
Blood sample for immunogenicity testing		✓		✓		
Vaccination		✓				
Provision of study supplies and instructions		✓				
Solicited Diary review			✓	✓		
Unsolicited/Concomitant Medications Diary review			✓	✓		
Assessment for cellulitis-like reaction, influenza-like illness (<i>if applicable</i>) ²		← ✓ →				
Review of adverse events and concomitant medications	← ✓ →					
Review of SAEs and AESIs (<i>if applicable</i>)	← ✓ →					

Notes to the schedule of assessments:

¹ These may be performed on or up to 7 days before the day of vaccination.

² Elevated axillary temperature of $\geq 99.5^{\circ}\text{F}$ ($\geq 37.5^{\circ}\text{C}$) (or a clear history of fever/chills), and at least one respiratory symptom (including sore throat, cough, wheezing, rhinorrhea/rhinitis) and at least one systemic symptom (including myalgia, headache, malaise and fatigue, diarrhea, nausea and/or vomiting, loss of appetite, and irritability).

Schedule of Assessments – Two Dose Regimen

Assessment		Visit 1	Phone call	Visit 2	Phone call	Visit 3	Phone call	Phone call
	Pre-Study	Vaccination	Diaries Reminder	Vaccination	Diaries Reminder	Exit Visit	SAE Follow-up	SAE Follow-up
	Day -7 to -1	Day 1	Day 3 + 2	Day 29 + 4	Day 3 + 2 after 2 nd dose	Day 29 + 4 after 2 nd dose	Day 90 + 7 after 2 nd dose	Day 180 + 7 after 2 nd dose
Invitation to participate	✓ ¹							
Informed consent	✓ ¹							
Demographics and influenza vaccination history	✓ ¹							
Medical history and baseline medication use	✓ ¹							
Targeted physical examination (<i>if necessary</i>)	✓ ¹			✓		✓		
Body weight	✓ ¹							
Axillary temperature		✓		✓				
Review of eligibility criteria		✓		✓				
Blood sample for immunogenicity testing		✓				✓		
Vaccination		✓		✓				
Provision of study supplies and instructions		✓		✓				
Solicited Diary review			✓	✓	✓	✓		
Unsolicited/Concomitant Medications Diary review			✓	✓	✓	✓		
Assessment for cellulitis-like reaction, influenza-like illness (<i>if applicable</i>) ²		←————— ✓ —————→						
Review of adverse events and concomitant medications		←————— ✓ —————→						
Review of SAEs and AESIs (<i>if applicable</i>)		←————— ✓ —————→						

Notes to the schedule of assessments: ¹ These may be performed on or up to 7 days before the day of vaccination. ² Elevated axillary temperature of $\geq 99.5^{\circ}\text{F}$ ($\geq 37.5^{\circ}\text{C}$) (or a clear history of fever/chills), and at least one respiratory symptom (including sore throat, cough, wheezing, rhinorrhea/rhinitis) and at least one systemic symptom (including myalgia, headache, malaise and fatigue, diarrhea, nausea and/or vomiting, loss of appetite, and irritability).

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AESI	Adverse Event of Special Interest
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
DO	Doctor of Osteopathy
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLM	Generalized Linear Model
GMFI	Geometric Mean Fold Increase
GMT	Geometric Mean Titer
HA	Hemagglutinin
HI	Hemagglutination Inhibition
ILI	Influenza-like Illness
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
NA	Neuraminidase
PPP	Per-Protocol Population
QIV	Quadrivalent Influenza Vaccine
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Seroconversion rate
SD	Standard Deviation
SDTM	Study Data Tabulation Model
Seqirus Pty Ltd	Seqirus Proprietary Limited
Seqirus QIV	Seqirus Split-virion Quadrivalent Influenza Vaccine

Seqirus TIV	Seqirus Split-virion Trivalent Influenza Vaccine
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIV	Trivalent Influenza Vaccine
TDOC	Sodium Taurodeoxycholate
US	United States of America
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. INTRODUCTION

Influenza is a highly infectious disease that occurs in epidemics throughout the northern and southern hemisphere winter months. The disease is characterized by the abrupt onset of respiratory and systemic symptoms, such as fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis [[Temte and Prunuske 2010](#)]. In general, influenza is resolved within two to seven days, although symptoms of cough and malaise may be prolonged. However, for some people, notably older adults and those with chronic diseases (such as pulmonary or circulatory disorders, metabolic disorders such as diabetes mellitus, renal dysfunction, or immunosuppression), influenza can exacerbate underlying medical conditions and/or lead to secondary viral or bacterial pneumonia [[Rothberg et al. 2008](#); [Fiore et al. 2009](#)]. During influenza epidemics, there is increased mortality among older adults (age > 65 years), people with chronic diseases and very young children (age 0 to 12 months), as well as an increase in morbidity and hospitalization because of influenza-associated complications [[Monto 2008](#), [Fiore et al. 2009](#)].

The influenza virus is an orthomyxovirus that can be classified into three types, A, B, and C, of which, type A and B viruses are the most clinically significant. The influenza type A virus can be further divided into subtypes based on the hemagglutinin (HA) and neuraminidase (NA) surface glycoprotein antigens. Of the influenza type A virus subtypes, the A/H3N2 and A/H1N1 subtypes are the most clinically important. Influenza type B viruses show extensive variation in antigenicity. Although only one subtype is known to exist, influenza type B viruses are separated into two distinct genetic lineages, Yamagata and Victoria.

Influenza vaccines are designed to protect against illness from the circulating virus strains. Hemagglutinin and, to some extent, neuraminidase antigens present in inactivated influenza vaccines are thought to act predominantly by inducing antigen-specific serum antibodies in vaccinated individuals. These antibodies can be protective against infection, or may result in less severe disease in some infected individuals.

Influenza vaccines for seasonal use since the 1960s have been trivalent, including variants of A/H3N2, A/H1N1, and one B-strain lineage. Monovalent vaccines have been produced in times of influenza pandemics, most recently in response to the 2009 H1N1 (Swine) Flu Virus. Recently, a number of quadrivalent vaccines have been licensed in the US, containing both B-strain lineages as well as variants of A/H3N2 and A/H1N1 subtypes.

1.1 BACKGROUND

1.1.1 Influenza B Virus Lineages

Two genetically distinct lineages of influenza B viruses have co-circulated since 1985 [[Rota et al. 1990](#)]. On average, influenza B strain accounts for approximately 25% of positive specimens in the US [[Ambrose and Levin, 2012](#)]. The burden of infection is largely school

age children, young adults and older adults [[Belshe 2010](#)]; however, young children experience the highest mortality with 34% of reported pediatric influenza deaths in the US due to B strain infections [Ambrose and Levin, 2012]. Mismatches between the B strain in the vaccine and the circulating strain occur in approximately 5 out of every 10 influenza seasons [[Belshe 2010](#)].

The Centers for Disease Control and Prevention (CDC) has estimated that in a season where there is a B strain mismatch, availability of quadrivalent influenza virus vaccines could have reduced annual influenza cases (range: 2200–970,000), hospitalizations (range: 14–8200), and deaths (range: 1–485) in the US [[Reed et al. 2012](#)].

1.1.2 2010 Southern Hemisphere Pediatric Febrile Adverse Events To Licensed CSL TIV

Note that Seqirus is now the owner of the split-virion trivalent influenza vaccine formerly known as CSL TIV.

In 2010, the CSL Southern Hemisphere trivalent influenza vaccine (TIV) formulation was associated in Australia and New Zealand with increased postmarketing reports of fever and febrile seizures in children [[Department of Health and Ageing 2010](#); [Centers for Disease Control and Prevention 2010](#)]. These reactions were predominantly in children between 6 months to <5 years of age. However, increased postmarketing reports of febrile reactions compared with historical averages were also observed in children 5 to < 9 years of age [[Centers for Disease Control and Prevention 2010](#)]. Since the 2010 Southern Hemisphere influenza vaccination season, CSL TIVs, including Afluria TIV, have not been approved for use in children < 5 years.

Before the 2010 Southern Hemisphere Pediatric Adverse Events (AEs), CSL TIV was approved for use in children from 6 months of age in several countries globally. CSL TIV was used in children 6 months and older in countries throughout the European Union since first Marketing Authorization in 2004. This indication was also registered in Australia and New Zealand in 2007 and marketed from 2008. Additionally, approvals were gained in Malaysia and Singapore in 2008 and Argentina in 2009, and marketed from 2009 in these countries for use in children from 6 months of age.

The 2010 Southern Hemisphere pediatric AEs were initially detected in the third year of a government sponsored pediatric influenza vaccination program in Western Australia (WA) in which CSL TIV was used. During the first two years of the WA program in which similar numbers of children were vaccinated only one febrile convulsion that was temporally related to TIV vaccination was reported [[Armstrong et al. 2011](#)].

An increased frequency of fever after receipt of 2009 CSL TIV compared to a US-licensed TIV among children 6 months to < 9 years of age was also observed in a clinical trial conducted in the United States [[Brady et al. 2014](#)]. The adverse event summary results from

this study for the two age groups 5 to < 9 years and 9 to < 18 years are also included in the Afluria TIV label.

Research conducted in 2010 using in-vitro modelling in a subgroup of children 5 years or younger with CSL TIV vaccine-related febrile convulsions, showed differences in cytokine production when peripheral blood mononuclear cells were stimulated with CSL TIV 2010 compared with TIVs from other manufacturers [[Blyth et al. 2011](#)]. This research thus demonstrated a potential clinical mechanism for the febrile adverse events, namely a pyrogenic response mediated by cytokines.

CSL and bioCSL conducted further intensive scientific investigations to identify the root cause of these AEs. Reports of the investigations, results, and conclusions have been presented to key regulatory agencies in countries where CSL TIV is licensed, including to the US Food and Drug Administration (FDA), and have been published [[Rockman, Becher et al. 2014](#), [Rockman, Dyson et al. 2014](#)].

The conclusions from the scientific investigations indicated that a combination of the following 3 key elements were predominant factors contributing to the 2010 Southern Hemisphere pediatric AEs:

- Strain changes, in particular, the replacement of all three virus strains in the 2009 Southern Hemisphere vaccine formulation with the new strains for 2010 Southern Hemisphere
- Degraded RNA fragments (predominantly < 200 nucleotides in length) that induced nuclear factor-kappa B (NF- κ B), a key cellular transcription factor in cytokine production, and
- Conformation of heat-sensitive viral components, such as lipids, which appeared to facilitate RNA delivery.

Although the presence of RNA appears to be the trigger for the febrile reactions, its delivery is key to the induction of the cytokine/chemokine signal and this appears to be dependent on the lipid level present in the final vaccine formulation. The lipid content is inversely proportional to the concentration of the detergent sodium taurodeoxycholate (TDOC), used to disrupt the virus [[Rockman, Becher et al. 2014](#)]. Characterization studies conducted examined the effect of varying the concentration of TDOC, used to split the virus during manufacture, on the NF- κ B activation response. Reduction of lipids using the above process appears to reduce facilitated RNA fragment delivery into cells, decreasing the NF- κ B induction that is associated with cytokine production. This may therefore reduce the potential for pyrogenic vaccine responses mediated by cytokines.

During the scientific investigations, the highest cytokine signal in the surrogate reactogenicity assays was generated by the B strain viruses, leading the company to focus on splitting conditions for B strains [[Rockman, Becher et al. 2014](#)]. Based on the available characterization data, the trivalent vaccines used in clinical trials starting from 2014, and in commercially supplied vaccines from 2014, have the B strain split at the upper levels of

TDOC concentration (1.5% w/v), which is within the company's registered splitting range for CSL TIV.

Following the conclusion of the scientific investigations after the 2010 Southern Hemisphere pediatric AEs, a clinical study (CSLCT-USF-10-69) was conducted in the United States in approximately 400 pediatric subjects 5 through 8 years of age, to prospectively evaluate the risk of febrile events and vaccine reactogenicity in subjects administered the 2014-2015 Northern Hemisphere formulation of CSL TIV or a US licensed comparator QIV. A post-hoc analysis involving pooled data across the 3 previous pediatric TIV clinical trials (CSLCT-USF-07-36, CSLCT-USF-06-29 and CSLCT-FLU-04-05) in the same pediatric age group as CSLCT-USF-10-69 was performed. The overall TIV fever rate in CSLCT-USF-10-69 was numerically lower compared to the historical data point estimates from the three studies. This suggests a reduction in overall fever rates after vaccination with TIV, the B strain now split with 1.5% w/v TDOC, compared to historical rates observed. As a result, all four vaccine strains used in Seqirus QIV studies starting from 2015 have been split using 1.5% w/v TDOC.

1.2 BACKGROUND INFORMATION ON SEQIRUS QIV

1.2.1 Overview

The Seqirus quadrivalent influenza virus vaccine (Seqirus QIV, formerly known as bioCSL QIV) is an inactivated, split-virion influenza virus vaccine formulated to contain 60 micrograms (mcg) HA per 0.5 mL dose in the recommended ratio of 15 mcg HA for each influenza virus strain: Type A (H1N1)-like virus; Type A (H3N2)-like virus; Type B (Victoria lineage) and Type B (Yamagata lineage). The Seqirus QIV formulation investigated in this study is consistent with the currently licensed Afluria trivalent influenza virus vaccine (split-virion TIV, formerly known as bioCSL TIV or CSL TIV), except for the addition of the alternate lineage influenza B strain which increases the total HA content from 90 to 120 mcg per mL.

As results from Study CSLCT-USF-10-69 with CSL TIV (using 1.5% TDOC w/v splitting for the B strain) indicated an overall reduction in fever rates (See [Section 1.1.2](#)), all four vaccine strains used in Seqirus QIV paediatric studies will be split using 1.5% w/v TDOC.

Development of a QIV, including B strains of both lineages, is expected to improve vaccine protection in target populations. Vaccine strain composition is based on the seasonal recommendations of the World Health Organization, which monitors circulating strains. TIVs contain antigens from the B-strain lineage predicted to be most prevalent. Such vaccines provide limited immunity against B strains of the lineage not included in the vaccine. A further problem with TIVs is that the predominant B-strain lineage has been unpredictable; between 2001 and 2011, B-strain lineage predictions for inclusion in vaccines were no better than chance alone [[Ambrose and Levin, 2012](#)].

1.2.2 Nonclinical Evaluation

Given the Seqirus QIV formulation is based on that of the company's split-virion TIV, with the exception of the additional B strain, Seqirus QIV is expected to have a similar safety profile to that established for the TIV. Seqirus considers that formal single- or repeat-dose safety/toxicology studies or a reproductive toxicity study using the Seqirus QIV formulation are not required, given all of the available characterization, clinical, and nonclinical data for the company's split-virion TIV and the adult clinical data for the company's QIV. Due to the extensive previous human experience, the predictive value of findings from animal studies is believed to be diminished in the context of the human experience with this company's TIV and QIV gained thus far.

The company has conducted a formal nonclinical toxicology study of the split-virion TIV; an embryofetal development study with postnatal evaluation of toxicity in rats. This study showed no observed adverse effects on mating, female fertility, pregnancy, parturition, lactation parameters, embryofetal or preweaning development; see the Investigator's Brochure for more detailed information.

1.2.3 Previous Clinical Experience

Seqirus QIV is an investigational product previously studied in adults and older adults in 2014 (Study CSLCT-QIV-13-01), and in children 5 through 17 years of age in 2015 (Study CSLCT-QIV-13-02).

Study CSLCT-QIV-13-01 was a phase 3, randomized, multicenter, double-blinded noninferiority study to evaluate the immunogenicity and safety of Seqirus QIV in comparison with the company's 2014-2015 US-licensed TIV formulation (referred to here as TIV-1), and a TIV containing the alternate B strain (referred to as TIV-2), in adults 18 years of age and above.

A total of 3485 subjects were randomized to receive either Seqirus QIV (1742 subjects), TIV-1 (871 subjects) or TIV-2 (872 subjects).

Demographics and key baseline characteristics of the study population were balanced between treatment groups. In adults 18 years and older, Seqirus QIV was not inferior to both TIVs based on adjusted GMTs (upper limit of the 2-sided 95% confidence interval [CI] for the GMT ratio [TIV/QIV] ≤ 1.5) and seroconversion rates (upper limit of the 2-sided 95% CI on difference of the TIV minus QIV $\leq 10\%$). Additionally, noninferiority was shown in both age sub-groups, 18 through 64 years, and 65 years and older, for all strains for both noninferiority endpoints.

Immunologic superiority of the alternate B strain was demonstrated overall, and for both age sub-groups.

There was no evidence that the addition of the second B strain resulted in immune interference to other strains included in the vaccine.

The safety profile of Seqirus QIV in study CSLCT-QIV-13-01 was consistent with the known safety profile of the company's TIV. The proportions of subjects with any solicited local adverse reaction were similar (QIV [37.4%], TIV-1 [34.6%], and TIV-2 [36.6%]), with the most common local adverse reaction being injection site pain (35.3%). More subjects 18 through 64 years of age experienced injection site pain [47.5%], than did subjects ≥ 65 years of age (23.2%). Proportions of subjects with any solicited systemic adverse event were also similar across the three study vaccine groups (QIV [28.9%], TIV-1 [28.4%], and TIV-2 [27.2%]). The most common systemic adverse events were myalgia and headache (18.7% and 13.6% of subjects, respectively). More subjects 18 through 64 years of age [37.2%] experienced any solicited systemic adverse events than did subjects ≥ 65 years of age (18 [19.6%]). Across all three study vaccine groups, a similar profile was observed for unsolicited adverse events; with headache being most commonly reported (in $< 4\%$ of subjects).

During the study period (up to 180 days postvaccination), a total of 66 subjects overall (1.9%) experienced 89 serious adverse events (SAEs). Of these, 4 SAEs (asthma, pancreatitis acute, hypoxia and pneumonia), in 3 subjects were considered related to administration of study product by the Investigator.

There were 6 deaths reported in the study and 5 were considered unrelated to vaccination. One death of pneumonia in the ≥ 65 years age cohort was assessed as related to the study vaccine by the Investigator. The Investigator commented that there was a possible relationship between the administration of the vaccine and the subject's subsequent adverse event. The possible mechanism could be an idiosyncratic inflammatory or immune reaction to any of the vaccine ingredients which contributed to respiratory compromise in a subject with pre-existing lung disease.

Study CSLCT-QIV-13-02 is an ongoing phase 3, randomized, multicenter, observer-blinded, noninferiority study to evaluate the immunogenicity and safety of Seqirus QIV with a US-Licensed 2015-2016 quadrivalent inactivated comparator influenza vaccine (Comparator QIV) in a pediatric population 5 through 17 years of age.

1.3 STUDY OVERVIEW

The present study is a phase 3, randomized, multicenter, observer-blinded study to evaluate the immunogenicity and safety of Seqirus QIV in comparison with a US-licensed 2016-2017 quadrivalent influenza vaccine (Comparator QIV) in children 6 months through 59 months of age. Seqirus QIV is intended for active immunization against influenza disease caused by influenza virus subtypes A and types B present in the vaccine. In the US, routine annual influenza vaccination of all persons 6 months of age and older continues to be recommended [[Centers for Disease Control and Prevention, 2013](#)].

The study will be conducted during the 2016-2017 Northern Hemisphere influenza immunization season in male and female children 6 months through 59 months of age. Subjects will be randomized to either treatment group in a 3:1 ratio (Seqirus QIV: Comparator QIV). The randomization will be stratified by age stratum into two study cohorts (Cohort A: 6 months through 35 months of age, and Cohort B: 36 months through 59 months of age). Age stratification will employ a quota to ensure that no more than 60% of the total sample subjects are represented in each age stratum. An interactive response technology (IRT) system will be used for subject randomization.

Subjects will receive either one or two doses of Study Vaccine (Seqirus QIV or Comparator QIV) as clinically indicated, depending on their previous history of influenza virus vaccination, in accordance with influenza vaccination dose recommendations of the US Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal Influenza with Vaccines. See [Section 3](#) for more information on the ACIP recommendations, dose and dosing regimen.

Immunogenicity assessment will occur prevaccination, and approximately 29 days after the last study vaccination dose by serological assessment with the hemagglutination inhibition (HI) assay. Safety monitoring will include solicited local reactions and systemic adverse events (reactogenicity) for 7 days following each study vaccination dose; unsolicited adverse events for at least 28 days following the last study vaccination dose; and cellulitis-like reactions for at least 28 days following the last study vaccination dose. Serious adverse events monitoring will continue for 180 days following the last study vaccination dose.

1.4 POTENTIAL RISKS AND BENEFITS

Influenza is a highly infectious disease that occurs in epidemics throughout the northern and southern hemisphere winter months. Influenza vaccines are designed to protect against illness from the circulating virus strains and have historically been trivalent, including variants of A/H3N2, A/H1N1, and one B-strain lineage.

Currently available TIVs contain antigens from the B-strain lineage predicted to be most prevalent. These vaccines provide limited immunity against B strains of the lineage not included in the vaccine. Therefore, Seqirus has developed a quadrivalent influenza vaccine (QIV), containing both B-strain lineages, for prophylaxis of influenza in adults, older adults and children. QIV is expected to improve overall vaccine protection in target populations, with a therapeutic benefit over TIV through reduction in the overall B strain influenza morbidity and mortality that should occur when intermittent mismatches between the B strain lineages in vaccines and circulating influenza are eliminated. Seqirus QIV is formulated to contain 120 mcg HA per mL in the recommended ratio of 30 mcg HA/mL for each influenza virus strain: type A/H1N1; type A/H3N2; type B (Victoria lineage); and type B (Yamagata

lineage). The vaccine has all four strains split at the upper levels of TDOC concentration (1.5% w/v).

CSLCT-QIV-15-03 will be the first pediatric study in children 6 months through 59 months of age conducted with Seqirus QIV. Given the similarities between Seqirus TIV and QIV formulations, the expected immunogenicity and safety profile of QIV in children 6 months through 59 months of age is substantially informed by previous QIV and TIV studies.

There is a long history of clinical and postmarketing use of the company's TIV. The safety of this TIV is supported by postmarketing surveillance data from more than [REDACTED] doses and from clinical study data. The clinical efficacy of CSL TIV against laboratory-confirmed influenza illness has been demonstrated in adults 18 to less than 65 years of age. The efficacy of CSL TIV for the prevention of laboratory-confirmed infection due to vaccine-matched strains during both seasons (2008 and 2009) was 60%, with a lower bound of the 95% CI of 41%.

The CSL TIV clinical development program has also shown that CSL TIV elicited a consistently robust immune response across all age groups, from six months of age and older. In children six months to less than 18 years of age and in older adults 65 years of age and older, the immune responses elicited by CSL TIV have been shown to be not inferior to that of a US-licensed seasonal influenza vaccine.

Postmarketing surveillance during the 2010 Southern Hemisphere influenza season suggested a disproportionate number of reports of febrile seizures and febrile events in children administered CSL TIV, compared to previous years. The reports were predominantly from children six months to less than five years of age [[Department of Health and Ageing 2010](#)]. However, increased rates of febrile reactions compared with historical averages were also observed in children 5 to < 9 years of age [[Centers for Disease Control and Prevention 2010](#)]. Following investigations into this safety signal, the approval for CSL TIV for use in children < 5 years of age was withdrawn in markets globally.

A TIV study (CSLCT-USF-10-69) was conducted in 2014 to inform QIV pediatric clinical development following the 2010 Southern Hemisphere pediatric influenza season spontaneous postmarketing adverse event reporting. The safety information from Study CSLCT-USF 10-69 regarding the risk of febrile events in pediatric subjects 5 through 8 years of age indicated reduction in overall and severe fever rates after vaccination with the 2014/2015 Northern Hemisphere formulation of TIV with the B strain split at the upper levels of TDOC concentration (1.5% w/v), compared to historical rates observed in previous pediatric clinical studies with the earlier formulation of TIV with the B strain split at a lower level of TDOC concentration. Overall, Study CSLCT-USF 10-69 demonstrated that the safety profile of this formulation of TIV is similar to that observed for the Comparator QIV, and both vaccines are generally well tolerated by study subjects.

Study CSLCT-QIV-13-01 demonstrated that Seqirus QIV formulated with the B strain split at the upper levels of TDOC concentration (1.5% w/v) elicited an immune response that was not

inferior to TIV-1 (containing the same virus strains as US-licensed Afluria), and TIV-2 (containing the alternate B strain) among adults ≥ 18 years of age. The safety profile of Seqirus QIV was similar to that of TIV-1 and TIV-2, and consistent with the known safety profile of Afluria.

The safety profile of Seqirus QIV in subjects 5 through 8 years of age will be further described by the ongoing study CSLCT-QIV-13-02

These studies are described in more detail in the Seqirus QIV Investigator's Brochure.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE AND ENDPOINT

2.1.1 Primary Objective

The primary objective of this study is to demonstrate that vaccination with Seqirus QIV elicits an immune response that is not inferior to the US-licensed comparator QIV (Comparator QIV) containing the same virus strains as Seqirus QIV among a pediatric population 6 months through 59 months of age.

2.1.2 Primary Endpoints

The immunogenicity of study vaccines will be assessed at least 28 days after the last vaccine administration by measuring the hemagglutinin inhibition (HI) antibody titers to the 4 viral strains included in the vaccines.

The noninferiority of Seqirus QIV compared to US licensed comparator QIV will be assessed by the 8 co-primary endpoints of geometric mean titer (GMT) and seroconversion rate (SCR) for each viral strain contained in the vaccines as follows:

- The GMT ratio* for the A/H1N1 strain;
- The GMT ratio for the A/H3N2 strain;
- The GMT ratio for the B strain (Yamagata lineage);
- The GMT ratio for the B strain (Victoria lineage);

- The difference between the seroconversion rates **for the A/H1N1 strain;
- The difference between the seroconversion rates for the A/H3N2 strain;
- The difference between the seroconversion rates for the B strain (Yamagata lineage);
- The difference between the seroconversion rates for the B strain (Victoria lineage).

**The GMT ratio is defined as the geometric mean of postvaccination (Study Exit Visit) HI titer for the US licensed comparator over the geometric mean of postvaccination (Study Exit Visit) HI titer for Seqirus QIV.*

***The rate of seroconversion is defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer \geq 1:40 or a prevaccination HI titer \geq 1:10 and a \geq 4-fold increase in postvaccination HI titer.*

2.2 SECONDARY OBJECTIVES AND ENDPOINTS

2.2.1 Secondary Objectives

The secondary objectives of the study are:

- 1 To assess the safety and tolerability of Seqirus QIV, in two age strata: 6 months through 35 months, and 36 months through 59 months, as well as overall.
- 2 To characterize the immunogenicity of Seqirus QIV and the US-licensed comparator QIV in two age strata: 6 months through 35 months, and 36 months through 59 months, as well as overall.

2.2.2 Secondary Endpoints

Secondary Safety Endpoints:

- Frequency and severity of solicited local reactions and systemic adverse events (AEs) for 7 days after each vaccination dose;
- Frequency of cellulitis-like reactions for at least 28 days after each vaccination dose;
- Frequency and severity of unsolicited AEs for at least 28 days after each vaccination dose;
- Frequency of serious adverse events (SAEs) for at least 180 days after the last vaccination dose.

Secondary Immunogenicity Endpoints:

The humoral immune response will be assessed in terms of HI antibodies for both the Seqirus QIV and Comparator QIV. Serum HI antibody titers against the 4 influenza vaccine strains will be used to calculate:

- Geometric mean titer (GMT): Geometric mean of HI titers prevaccination (Day 1) and postvaccination (Study Exit Visit);
- Seroconversion rate: Percentage of subjects with either a prevaccination HI titer $< 1:10$ and a postvaccination HI titer $\geq 1:40$ or a prevaccination titer $\geq 1:10$ and a ≥ 4 -fold increase in postvaccination titer;
- The percentage of subjects with a titer ≥ 40 (seroprotection rates) at Day 1 and Study Exit Visit;
- Geometric Mean Fold increase (GMFI)***: Geometric mean-fold-titer rise from Day 1 to Study Exit Visit.

***The rate of seroprotection is defined as the proportion of subjects with an HI titer $\geq 1:40$.

****GMFI in antibody titer is defined as the geometric mean of the fold increase of postvaccination HI antibody titer over the prevaccination HI antibody titer.

2.3 EXPLORATORY OBJECTIVE AND ENDPOINT

2.3.1 Exploratory Objective

To assess the frequency of antipyretic use in the first 7 days postvaccination in two age strata: 6 months through 35 months, and 36 months through 59 months, as well as overall according to treatment group.

2.3.2 Exploratory Endpoint

Frequency of antipyretic use in the 7 days after each vaccination dose.

3 STUDY DESIGN

3.1 STUDY DESIGN AND RATIONALE

This phase 3 study is a randomized, observer-blinded, comparator controlled study of Seqirus QIV, administered intramuscularly into the deltoid region or the anterolateral aspect of the thigh, versus a US licensed comparator QIV containing the same influenza strains recommended by the the US Food and Drug Administration (FDA) and Vaccines and Related Biological Products Advisory Committee (VRBPAC) for the 2016-2017 season. The study will be conducted during the 2016-2017 Northern Hemisphere influenza immunization season in male and female subjects 6 months through 59 months of age.

After parent(s)/guardian(s) have provided written informed consent (Visit 1 [Day 1]), eligible subjects will be stratified by age to one of two age cohorts:

- Cohort A comprising subjects 6 months through 35 months of age;
- Cohort B comprising subjects 36 months through 59 months of age.

The Interactive Response Technology (IRT) will include a quota for each age stratum so that no more than 60% of the total sample size is represented in each age stratum.

Subjects in the 36 through 59 months age group will be enrolled and randomized first until approximately one third of subjects (or a minimum of 300 subjects) in this age cohort have received the first vaccination and have had an opportunity to enter at least 7 days of safety data postvaccination. A safety data cut will then be performed, tables and listings produced and a Data and Safety Monitoring Board (DSMB) meeting convened to review and assess the available safety data.

Recruitment in the 36 through 59 months age cohort will not be halted during the period of the data cut and DSMB review. Enrollment in the younger age cohort (subjects 6 months through 35 months of age) will only commence after the DSMB has reviewed the safety data and recommended that the study may proceed.

A second safety data cut will be performed when approximately one third of subjects (or a minimum of 300 subjects) in the 6 through to 35 months age cohort have received the first vaccination and have had an opportunity to enter at least the 7 days of safety data postvaccination. A DSMB meeting will be convened once tables and listings are produced to review and assess the available safety data. Recruitment in the 6 through 35 months age cohort will not be halted during the period of the data cut and DSMB review.

After stratification, subjects will be randomized to one of the two treatment groups using a 3:1 allocation ratio to receive either Seqirus QIV or the US licensed comparator QIV ([Figure 1](#)).

Subjects will provide pre- and postvaccination serological specimens as well as structured safety follow-up.

Screening evaluations will be performed either the day of the vaccination or within a maximum of 1 week before vaccination and include medical history, and targeted physical examination (if clinically indicated). Vaccination will occur on Day 1. On Day 1 and prior to vaccination, a serum sample will be collected for influenza-specific serology.

The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in children 12 months through 35 months of age, or the deltoid muscle of the non-dominant arm in children 36 months through 59 months of age.

The parent(s)/guardian(s) of subjects will record electronically:

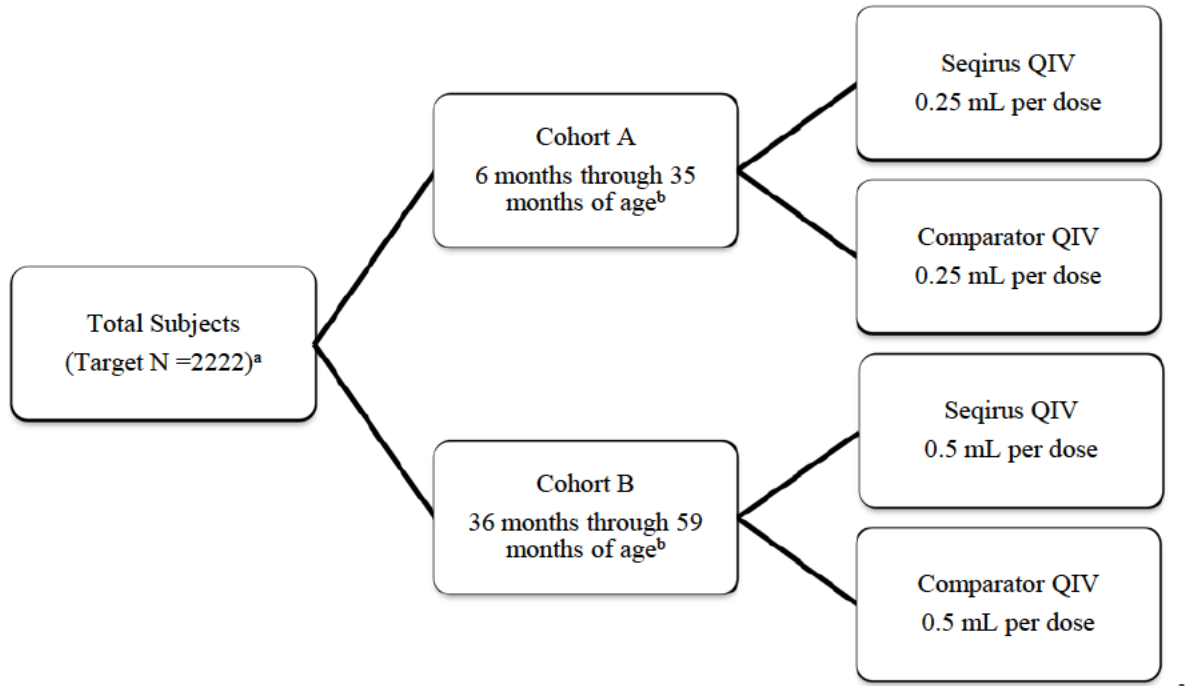
1. In a “7-Day Diary”, the occurrence of solicited AEs, a pre-specified series of local reactions and systemic symptoms and temperature that may occur between Day 1 and Day 7 after a vaccination.
2. In an “Other Body Symptoms Diary”, any unsolicited AEs that may occur between Day 1 and the Study Exit Visit.
3. In a “Medication Diary”, all concomitant medication use that may occur between Day 1 and the Study Exit Visit.

Subjects will return to the clinic 28 (+4) days after each indicated vaccine dose (Day 29 +4). During this visit, entries in the 7-Day Diary, the Other Body Symptoms Diary and the Medication Diary will be reviewed with the parent(s)/guardian(s) and a targeted physical examination performed as clinically indicated. For one-dose schedule subjects, Visit 2 (Day 29+4) post vaccination is the Exit Visit ([Figure 2](#)). For two-dose schedule subjects, Visit 3 (Day 29+4 post second vaccination) is the Exit Visit ([Figure 3](#)). SAEs and adverse events of special interest (AESIs) will be collected via a telephone call at least 90 days after the last vaccination dose (Day 90+7) and another at 180 days after the last vaccination dose (Day 180+7).

Analyses of safety data may be triggered by the DSMB if halting rule criteria are met in either study age cohort, or following ad-hoc requests for review by Seqirus as described in the DSMB Charter.

An interim analysis will be made once all subjects have completed all immunogenicity assessments and all solicited and unsolicited adverse event reporting, and results will be presented in an interim study report. A final clinical study report will present all immunogenicity and safety data collected from the active study period and safety data through to the final evaluation (180 days following the last vaccination dose).

Figure 1 Subject Stratification and Treatment Allocation Schema



^a allocated in 3:1 ratio, Seqirus QIV to Comparator QIV.

^b no more than 60% of the total sample size is represented in each age stratum.

Figure 2. Study Overview: Single Vaccination Regimen

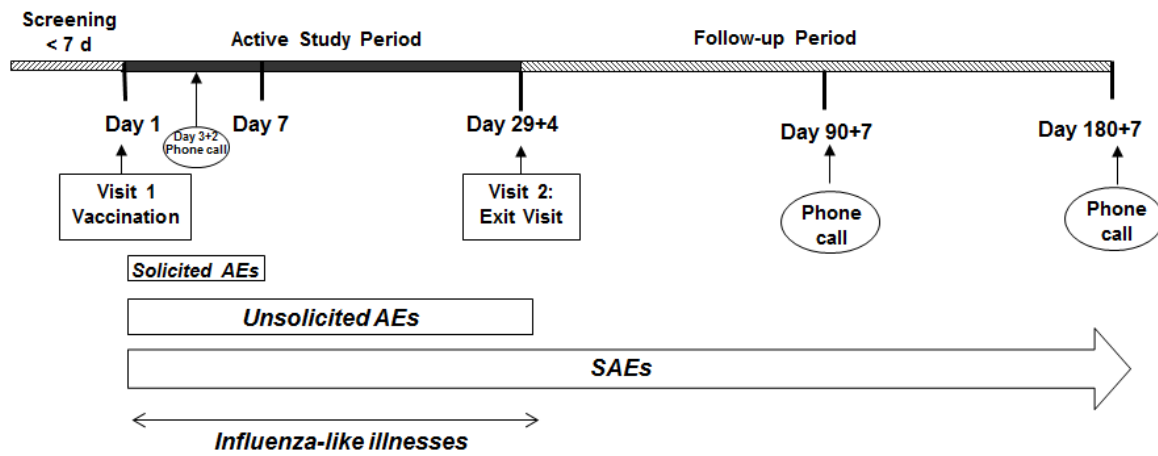
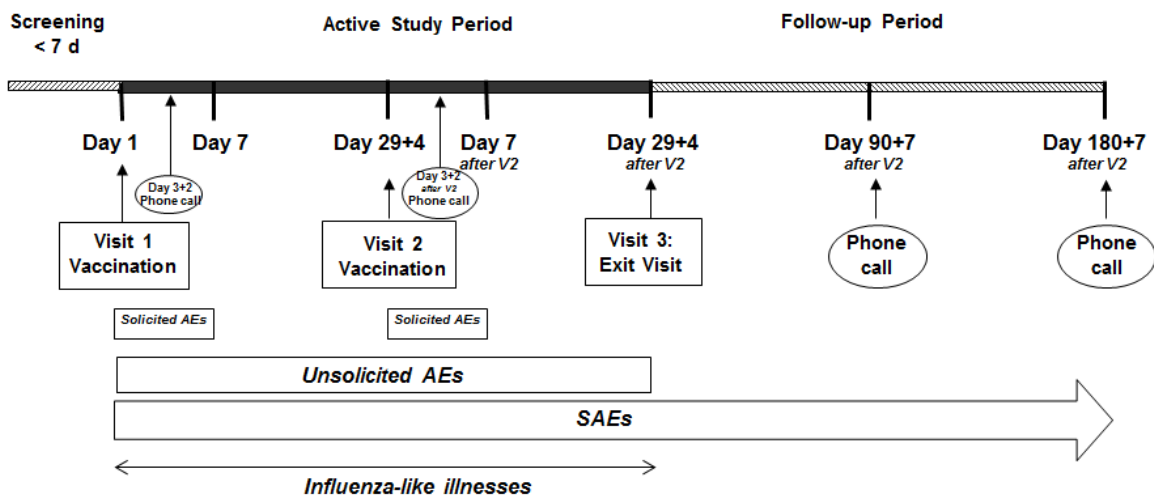


Figure 3. Study Overview: Two Vaccination Regimen



3.2 DOSE AND DOSING REGIMEN

Subjects who meet the entry criteria will stratified by age and then randomized to one of the two treatment groups using a 3:1 allocation ratio to receive either Seqirus QIV or the US licensed comparator QIV. Each subject will receive one 0.25 or 0.5 mL dose of Study Vaccine on Day 1. Subjects scheduled to receive a second dose will also receive one 0.25 or 0.5 mL dose of Study Vaccine after 28 days.

Cohort A, Subjects 6 months through 35 months of age will receive one or two 0.25 mL doses of Study Vaccine according to the current US Advisory Committee on Immunization Practices (ACIP) dosing recommendations. Each 0.25 mL dose contains 7.5 mcg hemagglutinin antigen (HA) from each of the following four influenza strains: A (H1N1)-like virus; A (H3N2)-like virus; B (Yamagata lineage) and B (Victoria lineage).

Cohort B, Subjects 36 months through 59 months of age will receive one or two 0.5 mL doses of Study Vaccine according to the current US Advisory Committee on Immunization Practices (ACIP) dosing recommendations. Each 0.5 mL dose contains 15 mcg hemagglutinin antigen (HA) from each of the following four influenza strains: A (H1N1)-like virus; A (H3N2)-like virus; B (Yamagata lineage) and B (Victoria lineage).

3.3 PLANNED STUDY DURATION

Study subjects will be scheduled to receive either a single vaccination or two-vaccination regimen as clinically indicated.

The maximum study duration for an individual subject receiving a single vaccination will be up to 7 months (up to 7 days screening period, 28+4 days active study period and 180+7 days safety follow-up period).

The maximum study duration for an individual subject scheduled for the two-vaccination regimen will be up to 8 months (up to 7 days screening period, 28+4 days active study period after each Study Vaccine dose, and 180+7 days safety follow-up period after the last vaccination dose).

The overall study duration (ie, first subject's screening visit to last subject's end of study visit) will be a maximum of 10 months.

3.4 PLANNED NUMBER OF SITES

The study is planned to be conducted at several investigational centers in North America.

3.5 PLANNED NUMBER OF SUBJECTS

This study will enroll approximately 2222 subjects. The Interactive Response Technology (IRT) will include a quota for each age stratum so that no more than 60% of the total sample size is represented in each age stratum. After stratification, subjects will be randomized to one of the two treatment groups using a 3:1 allocation ratio to receive either Seqirus QIV or the US licensed comparator QIV.

3.6 STUDY MONITORING PROCEDURES

3.6.1 Data and Safety Monitoring Board

An independent DSMB will monitor subject safety during the study. The DSMB will comprise clinical study experts with experience in vaccine studies and safety assessment. The DSMB will provide recommendations for stopping or continuing the study based on the assessment of study safety data according to processes defined in the study protocol and the DSMB Charter.

DSMB will review available safety data and provide recommendations after approximately one third of subjects (or a minimum of 300 subjects) in the 36 through 59 months age group have received the first vaccination and have had an opportunity to enter at least 7 days of safety data postvaccination.

A second safety data cut will be performed when approximately one third of subjects (or a minimum of 300 subjects) in the 6 through to 35 months age cohort have received the first vaccination and have had an opportunity to enter at least 7 days of safety data postvaccination. A DSMB meeting will be convened once tables and listings are produced to review and assess the available safety data. Recruitment in both age cohorts will not be halted during the period of the data cut and DSMB review.

Adverse events contributing to enrollment halting rules (see [Section 9.7](#)) will be reported to the Sponsor automatically from the electronic Case Report Form (eCRF) in the clinical database. If enrollment halting rules are met, enrollment into the study will be halted pending DSMB review of the safety data, and Sponsor consideration of DSMB recommendations following the review. Independent safety monitors at each site are not required.

The DSMB will:

- Be responsible for providing recommendations to Seqirus surrounding study conduct matters that affect safety.
- Review the safety data at designated time points and potentially ad-hoc time points and identify if significant safety concerns arise during the study.
- Review data that may affect subject continuation.
- Make recommendations regarding study progression.

The DSMB will be constituted and conducted in accordance with the FDA *Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical Trial Data and Monitoring Committees. March 2006.*

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 ELIGIBILITY CRITERIA

The study population will be selected on the basis of the inclusion and exclusion criteria described in the sections below. Subject eligibility should be reviewed and documented by an appropriately medically qualified member of the investigator's study team before subjects are included in the study.

4.1.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to participate in this study:

1. Male or female subject 6 months through to 59 months of age at the time of first vaccination and born between 36 and 42 weeks of gestation;
2. Parent or legally acceptable representative able to provide written informed consent and be willing and able to adhere to all protocol requirements including blood draws;
3. Subject is in generally good health as per the Investigator's medical judgment.

4.1.2 Exclusion Criteria

If one or more of the following exclusion criteria are met, the subject will be ineligible to take part in this study:

1. History of allergic reactions to egg proteins or any components of the Study Vaccines;
2. History of serious adverse reactions to any influenza vaccines;
3. History of Guillain-Barré syndrome or other demyelinating disease such as encephalomyelitis and transverse myelitis;
4. History of licensed or investigational influenza vaccination in the last 6 months;
5. Clinical signs of active infection and/or an axillary temperature of $\geq 99.5^{\circ}\text{F}$ / $\geq 37.5^{\circ}\text{C}$ on the day of vaccination or within 48 hours preceding vaccination. Study entry may be deferred for such individuals, at the discretion of the Investigator;
6. Current or recent, acute or chronic medical conditions that in the opinion of the Investigator are clinically significant and/or unstable (such as illness exacerbations) which within the preceding 30 days:
 - a) required hospitalization; or
 - b) associated with significant organ function deterioration; or
 - c) associated with major changes to treatment dosages due to disease instability*; or
 - d) required major new treatments.

**recent changes to treatments not related to disease instability, such as routine summer dose reductions to agents for attention deficit hyperactivity disorder (ADHD) are permitted.*

7. History of any seizures, with the exception of a single febrile seizure;
8. Self-reported or known seropositivity suggestive of acute or chronic viral infection for human immunodeficiency virus, hepatitis B or hepatitis C;
9. Known or suspected congenital or acquired immunosuppressive conditions;
10. Current or recent immunosuppressive or immunomodulatory therapy, as follows:
 - a) Chronic (> 2 weeks) or long-term systemic corticosteroids: ≥ 0.125 mg/kg/day of oral prednisolone or equivalent daily;
 - b) Sporadic systemic corticosteroids: ≥ 0.5 mg/kg/day of oral prednisolone or equivalent for two or more short courses of > 3 days in the 3 months preceding vaccination;

Note: Use of topical or inhaled corticosteroids prior to administration of the Study Vaccine or throughout the study is acceptable.

11. Current or medical history of malignant neoplasms;
12. Administration of immunoglobulin and/or any blood products within the previous 90 days preceding the administration of the Study Vaccine or planned administration during the study;
13. Participation in a clinical trial or use of an investigational compound (ie, a new chemical or biological entity not registered for clinical use, including investigational vaccines) within 28 days prior to or 28 days after receiving the Study Vaccine, or plans to enter a study during this period;
14. Vaccination with a licensed vaccine 21 days (for live or inactivated vaccines) prior to receiving the Study Vaccine, or plans to receive any licensed vaccine prior to the Study Exit Visit;
15. Medical conditions or treatments contraindicating intramuscular vaccination due to increased risk of bleeding. These may include known bleeding disorders (such as thrombocytopenia), or treatment with anticoagulants (such as warfarin) in the 3 weeks preceding vaccination. However, antiplatelet agents such as low-dose aspirin, ticlopidine (Ticlid) and clopidogrel (Plavix) are permitted;
16. Family members of the employees of the Investigator or study center with direct involvement in the study, or with other clinical studies under the direction of that Investigator or study center.

4.2 SUBJECT WITHDRAWAL

4.2.1 Subject Withdrawal

Subjects may withdraw from the study at any time at their own request or request of the parent or legally appropriate representative, or they may be withdrawn at any time at the discretion of the investigator or Seqirus for safety, behavioral or administrative reasons (eg,

due to an adverse event, protocol deviation, loss to follow-up, subject noncompliance to protocol procedures, and study termination).

A subject is considered lost to follow-up after three (3) documented failed attempts to contact the parent(s)/guardian(s) or legally appropriate representative on three (3) separate days.

In accordance with ICH principles of Good Clinical Practice (GCP) the investigator always has the option to advise a subject to withdraw from the study if the subject's safety or well-being is compromised by his or her further participation in the study. Concern for the interests of the subject must always prevail over the interests of the study.

If a subject is withdrawn from the study or further participation is declined, they will continue to have access to medical care and will be treated as per routine medical practice.

4.2.2 Procedures for Handling Withdrawals

If a subject or parent/ legally appropriate representative declines further participation or is withdrawn from the study, attempts will be made to complete and document the final assessment. If the subject is withdrawn from the study after receiving Study Vaccine, every effort will be made to ensure that the relevant safety assessments are completed. The subject may also be asked by the investigator to complete other study assessments.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, Seqirus may retain and continue to use any data collected before such withdrawal of consent.

In the event that a subject withdraws from the study, the investigator should record the reason and date of withdrawal in the electronic case report form (eCRF) and in the subject's medical records.

4.2.3 Replacement Policy

Subjects withdrawn from the study will not be replaced. However, if there are a significant number of withdrawals not related to the administration of Study Vaccine, a decision will be made as to whether withdrawn subjects will be replaced.

5 STUDY INTERVENTIONS

5.1 DESCRIPTION OF INVESTIGATIONAL PRODUCT(S)

5.1.1 Seqirus Split-virion Quadrivalent Influenza Vaccine (Seqirus QIV)

Substance number	Seqirus QIV
Active substance	Inactivated Split-virion, Quadrivalent Influenza Vaccine
Trade name	Not Applicable
Dosage forms	A single 0.25 mL dose of Seqirus QIV in a prefilled needleless syringe. A single 0.5 mL dose of Seqirus QIV in a prefilled needleless syringe.
Doses	A single 0.25 mL dose of Seqirus QIV containing a total of 30 mcg of HA. A single 0.5 mL dose of Seqirus QIV containing a total of 60 mcg of HA.
Mode of administration	Intramuscular injection into the deltoid region of the arm or the anterolateral aspect of the thigh.

Seqirus QIV is an inactivated, split-virion, thimerosal-free, quadrivalent influenza vaccine, administered as one 0.25 mL or 0.5 mL intramuscular dose into the deltoid muscle or the anterolateral aspect of the thigh. The vaccine is presented in a prefilled needleless syringe and is manufactured by Seqirus Australia in accordance with GMP guidelines and local regulatory requirements.

Each 0.25 mL dose will contain 7.5 mcg HA from each of the following four influenza strains (recommended by the FDA's VRBPAC for the 2016-2017 influenza season in the US):

- 7.5 mcg per 0.25 mL dose **A/California/7/2009 (H1N1)pdm09-like virus;**
- 7.5 mcg per 0.25 mL dose **A/Hong Kong/4801/2014 (H3N2)-like virus;**
- 7.5 mcg per 0.25 mL dose **B/Brisbane/60/2008-like virus (B/Victoria lineage);**
- 7.5 mcg per 0.25 mL dose **B/Phuket/3073/2013-like virus (B/Yamagata lineage).**

Each 0.5 mL dose will contain 15 mcg HA from each of the following four influenza strains (recommended by the FDA's VRBPAC for the 2016-2017 influenza season in the US):

- 15 mcg per 0.5 mL dose **A/California/7/2009 (H1N1)pdm09-like virus;**

- 15 mcg per 0.5 mL dose **A/Hong Kong/4801/2014 (H3N2)-like virus**;
- 15 mcg per 0.5 mL dose **B/Brisbane/60/2008-like virus** (*B/Victoria lineage*);
- 15 mcg per 0.5 mL dose **B/Phuket/3073/2013-like virus** (*B/Yamagata lineage*).

5.1.2 Comparator Product

Substance number	Comparator QIV
Active substance	Inactivated Split-virion, Quadrivalent Influenza Vaccine
Trade name	Fluzone Quadrivalent
Dosage form	A single 0.25 mL dose of Comparator QIV in a prefilled needleless syringe. A single 0.5 mL dose of Comparator QIV in a prefilled needleless syringe.
Dose	A single 0.25 mL dose of Comparator QIV containing a total of 30 mcg of HA. A single 0.5 mL dose of Comparator QIV containing a total of 60 mcg of HA.
Mode of administration	Intramuscular injection into the deltoid region of the arm or the anterolateral aspect of the thigh.

The US-licensed Comparator QIV will be an inactivated, split-virion, thimerosal-free, quadrivalent influenza vaccine, administered as one 0.25 mL or 0.5 mL intramuscular dose into the deltoid muscle or the anterolateral aspect of the thigh. The vaccine is presented in a prefilled needleless syringe.

Each 0.25 mL dose will contain 7.5 mcg HA from each of the following four influenza strains (recommended by the FDA's VRBPAC for the 2016-2017 influenza season in the US):

- 7.5 mcg per 0.25 mL dose **A/California/7/2009 (H1N1)pdm09-like virus**;
- 7.5 mcg per 0.25 mL dose **A/Hong Kong/4801/2014 (H3N2)-like virus**;
- 7.5 mcg per 0.25 mL dose **B/Brisbane/60/2008-like virus** (*B/Victoria lineage*);
- 7.5 mcg per 0.25 mL dose **B/Phuket/3073/2013-like virus** (*B/Yamagata lineage*).

Each 0.5 mL dose will contain 15 mcg HA from each of the following four influenza strains (recommended by the FDA's VRBPAC for the 2016-2017 influenza season in the US):

- 15 mcg per 0.5 mL dose **A/California/7/2009 (H1N1)pdm09-like virus**;
- 15 mcg per 0.5 mL dose **A/Hong Kong/4801/2014 (H3N2)-like virus**;
- 15 mcg per 0.5 mL dose **B/Brisbane/60/2008-like virus** (*B/Victoria lineage*);
- 15 mcg per 0.5 mL dose **B/Phuket/3073/2013-like virus** (*B/Yamagata lineage*).

5.2 PACKAGING, LABELING, SUPPLY AND STORAGE

5.2.1 Packaging and Labeling

The Study Vaccine will be packaged and labeled according to current International Conference on Harmonisation (ICH) Good Manufacturing Practice and GCP guidelines, and national legal requirements.

The manufacture and labeling of the Study Vaccine will comply with specific US Regulatory requirements.

5.2.2 Supply and Storage

The Study Vaccines will be supplied to the study sites by Seqirus or a third party vendor contracted by Seqirus. Syringes will be labeled and boxed in individual cartons.

The Study Vaccines should be stored under temperature monitored conditions (+36°F to +46°F [+2°C to +8°C]) in a secure area. Under no circumstances should the vaccines be frozen, as this may disrupt the antigenic immunogenicity of the viral proteins. If the container contents are frozen, or suspected to have been frozen, the product should not be used. In order to protect from light, the vaccine must be stored in its original carton until time of administration.

5.3 ACCOUNTABILITY AND DESTRUCTION

Initial shipments of Study Vaccine will be shipped to the investigational study sites on confirmation that regulatory and Institutional Review Board (IRB) requirements have been met and will be available prior to study start. Upon receipt of the Study Vaccine, the Investigator/delegate will conduct an inventory and acknowledge receipt of the product.

Study Vaccines must only be used for subjects enrolled in this clinical study. The appropriately qualified unblinded site staff member administering the Study Vaccine must record the dispensing details on the Study Vaccine Administration Form provided. On completion of the study, delivery records will be reconciled with those of used and unused Study Vaccine.

Used syringes are to be disposed of immediately after use in appropriate sharps containers. Used cartons are to be retained for accountability purposes and are to be destroyed at site after final accountability/reconciliation has been completed at the site. Unused vaccines are to be returned to the third party vendor responsible for vaccine management for final disposal or destroyed at site provided a certificate of destruction is supplied. All relevant disposal documentation, including the certificate of destruction, will be filed in the TMF and a copy filed-in the investigational site files.

Information on the destruction of the Study Vaccine is provided in the Pharmacy Manual.

5.4 OTHER INTERVENTION(S)

Not applicable.

5.5 RESCUE THERAPY

Not applicable.

6 ALLOCATION, DOSING AND ADMINISTRATION

6.1 ALLOCATION TO TREATMENT

6.1.1 Subject Assignment

After providing written informed consent, the subject will be issued with a study-level unique subject identification number. The subject identification number will be used to identify the subject for the duration of the study. Subject identification numbers will not be reassigned or reused.

6.1.2 Randomization Procedures

A randomization scheme will be used to ensure that the balance between the treatment groups is maintained. To ensure the study blind is maintained, delegates from the Interactive Response Technology (IRT) company, in association with a Seqirus statistician/delegate not directly involved in the analysis of study results, will prepare the study randomization code. The Stability and Environmental Monitoring group at Seqirus will keep a checked final copy of the randomization code on file. Emergency Code Break IRT access will be provided to the investigational site for use in case of an emergency.

Subjects in the 36 through 59 months age group will be enrolled and randomized first until approximately one third of subjects (or a minimum of 300 subjects) in this age cohort have received the first vaccination and have had an opportunity to enter at least 7 days of safety data postvaccination. A safety data cut will then be performed and a DSMB meeting convened to review and assess the available safety data. Recruitment in the 36 through 59 months age cohort will not be halted during the period of the data cut and DSMB review. Enrollment in the younger age cohort (subjects 6 months through 35 months of age) will only commence after the DSMB has reviewed the safety data and recommended that the study may proceed.

A second safety data cut will be performed when approximately one third of subjects (or a minimum of 300 subjects) in the 6 through to 35 months age cohort have received the first

vaccination and have had an opportunity to enter at least 7 days of safety data postvaccination. A DSMB meeting will be convened once tables and listings are produced to review and assess the available safety data. Recruitment in the 6 through 35 months age cohort will not be halted during the period of the data cut and DSMB review.

Eligible subjects will be randomized by means of IRT to one of the 2 treatment groups in a 3:1 ratio (Seqirus QIV: Comparator QIV) and will be proportionally balanced in the two age strata (6 through 35 months and 36 through 59 months), with no more than 60% of the total sample size represented in one age stratum. The IRT system will manage randomization and provide to the sites a subject randomization number. The number will correspond to the appropriate study treatment.

The Investigator will be supplied with a user guide for the IRT.

6.1.3 Blinding Procedures

6.1.3.1 *Blinding Method*

Investigational site staff including the investigator and all personnel performing study assessments will be blinded to treatment allocation (observer-blind). The subject and parent(s)/ guardian(s) will also remain blinded to treatment allocation.

As there may be a visual difference between the Seqirus QIV and the Comparator QIV pre-filled syringes, personnel who prepare and administer the Study Vaccine will be considered unblinded and excluded from involvement in other study procedures, with the exception of other Study Vaccine related activities, such as receipt, preparation and accountability management.

All Seqirus study staff, excluding those in the Seqirus Stability and Environmental Monitoring group and Quality Assurance group, will also be blinded to treatment allocation. Study monitors will be blinded to subject treatment allocation and will remain blinded when performing Study Vaccine accountability.

6.1.3.2 *Breaking the Blind for an Emergency*

The randomization code for individual subjects may be unblinded to a site via the IRT system during the study in emergency situations for reasons of subject safety, if knowing the treatment assignment will change subject management. Whenever possible, the Investigator should consult with the Medical Monitor before unblinding the randomization code. The reason for unblinding the randomization code must be fully documented and the Investigator must follow the defined procedures provided in the Study Manual.

6.1.3.3 *Planned Unblinding Procedures*

The randomization code will be unblinded four times:

1. at the time of the safety analysis after a third of subjects or a minimum of 300 subjects in the 36 months through 59 months of age cohort have been enrolled;
2. at the time of the safety analysis after a third of subjects or a minimum of 300 subjects in the 6 months through 35 months of age cohort have been enrolled
3. at the time of the interim analysis when all subjects have completed all immunogenicity assessments and all solicited and unsolicited adverse event reporting;
4. and finally, once all data (including extended follow-up for recording SAEs and AESIs) have been entered into the study database for each subject and the database has been locked.

The randomization code will be provided to the Biostatistics group once written authorization of database lock has been received.

The first unblinding will occur after a third of subjects or a minimum of 300 subjects in the 36 months through 59 months of age cohort are enrolled. The DSMB will review and assess available unblinded safety data in a closed session. The Seqirus team will remain blinded.

The second unblinding will occur after a third of subjects or a minimum of 300 subjects in the 6 months through 35 months of age cohort are enrolled. The DSMB will review and assess available unblinded safety data in a closed session. The Seqirus team will remain blinded.

Unblinding of the randomization code will also occur once all subjects have completed all immunogenicity assessments and all solicited and unsolicited adverse event reporting. This will facilitate timely analysis of immunogenicity and safety data including all solicited AEs. The results may be communicated to regulatory authorities and relevant personnel within Seqirus but not to personnel directly involved in monitoring the study or interacting with investigators. The results will not be communicated to investigators.

A final clinical study report will present all immunogenicity and safety data collected from the active study period and safety data through to the final evaluation (180 days following the last vaccination dose).

Seqirus Safety personnel may unblind the randomization code for an individual subject at any time to facilitate assessment of suspected unexpected serious adverse reactions (SUSARs) experienced by any subject for expedited reporting to regulatory authorities. To maintain integrity of the study blind the Seqirus Safety personnel responsible for assessment of SUSARs are excluded from the Seqirus study team.

6.2 DOSING AND ADMINISTRATION

An appropriately qualified unblinded site staff member will dispense and administer the Study Vaccine as a 0.25 or mL 0.5mL intramuscular dose as appropriate into either right or left deltoid muscle or into the anterolateral aspect of the thigh, according to the randomization code and the age of the subject. Prior to administering a study vaccine the prefilled syringe should be shaken thoroughly and inspected visually for particulate matter and discoloration. If either of those conditions exist, the study vaccine should not be administered. Where possible, the injection will be administered into the contralateral arm to which the blood sample was drawn, unless there is a medical reason which dictates both need to be conducted on the same arm. This reason should be documented in source, if applicable.

The use of topical anesthetic cream (eg, EMLA Cream) on the vaccination site before or after administration of the Study Vaccine is prohibited.

6.3 TREATMENT COMPLIANCE

Not applicable. Study Vaccine will be administered by site staff.

7 CONTRAINDICATIONS, PERMITTED THERAPIES AND PROHIBITED THERAPIES

7.1 CONTRAINDICATIONS AND PRECAUTIONS TO FURTHER DOSING

Administration of the second vaccination will be postponed in the event individual subject is experiencing clinical signs/symptoms of active infection and/or axillary temperature of $\geq 99.5^{\circ}\text{F}$ ($\geq 37.5^{\circ}\text{C}$) on the day of vaccination or within 48 hours preceding vaccination. Vaccination also will be postponed if individual subject used a prophylactic antipyretic on the day of vaccination.

Administration of the second vaccination to individual subjects will be contraindicated in the event of:

1. Axillary temperature of greater than 103.1°F (39.5°C) within 48 hours of the first vaccination, and assessed as related to study vaccination;
2. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of the first vaccination, and assessed as related to study vaccination;
3. Seizures with or without fever after the first vaccination, and assessed as related to study vaccination;
4. Any other event related to the Study Vaccine, and considered by the Investigator and/or the Sponsor to be clinically significant, and which would suggest significant hazard with further administration of Study Vaccine.

Subjects who are contraindicated to receive the second vaccination should complete an Exit Visit for assessment by the Investigator/ delegate.

7.2 PERMITTED THERAPIES

Therapies not listed in Section 7.3 below are permitted during the study.

7.3 PROHIBITED THERAPIES

Subjects are not to be enrolled into the study if they receive any prohibited therapy or any therapy in a prohibited dosage that cannot be discontinued or reduced to a permitted dose before enrollment. Therapies not listed below are permitted.

The following therapies are NOT PERMITTED before and/or during the active study period (Day 1 to Exit Visit) for the periods outlined below and as specified in the study exclusion criteria:

- Current or recent immunosuppressive or immunomodulatory therapy, as follows:
 - Chronic or long term systemic corticosteroids: ≥ 0.125 mg/kg/day of oral prednisolone or equivalent daily;
 - Sporadic systemic corticosteroids: ≥ 0.5 mg/kg/day of oral prednisolone or equivalent for one or more short courses of > 3 days in the three months preceding vaccination and/or during the active study period.
- Administration of immunoglobulin and/or any blood products within the 3 months preceding study vaccination, or planned administration during the active study period;
- Participation in a clinical trial or use of an investigational compound (ie, a new chemical or biological entity not licensed for clinical use) within 28 days prior to the first dose of Study Vaccine, or within 28 days after receiving the final indicated dose of Study Vaccine, or plans to enter a clinical trial during this period;
- Vaccination with a licensed or investigational influenza vaccine within the 6 months prior to receiving the first dose of Study Vaccine and during the study;
- Vaccination with a licensed live or inactivated vaccine 21 days prior to receiving the Study Vaccine, or plans to receive any licensed vaccine prior to the Study Exit Visit;
- Treatment with warfarin or other anticoagulants in the 3 weeks preceding vaccination, contraindicating intramuscular vaccination (with the exception of antiplatelet agents).
- Prophylactic antipyretics on the day of vaccination or for the first 7 days postvaccination. Antipyretic use for the treatment of AEs during the study period is permitted, and will be documented as concomitant medications.
- The use of topical anesthetic cream (eg, EMLA Cream) on the vaccination site before or after administration of the Study Vaccine is prohibited. Topical anesthetic cream use at the blood draw site is permitted.

If any of the above therapies are received during the active study period, the subject will not be withdrawn from the study unless required for medical reasons, but immunogenicity results pertaining to this subject may be excluded from assessment prior to unblinding following medical review of the potential for the therapies to impact on immunogenicity results.

7.4 DIETARY AND LIFESTYLE RESTRICTIONS

Not applicable.

7.5 OVERDOSE

Overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An overdose that does not result in any adverse signs or symptoms should not be considered an AE. The effects of any potential overdose with QIV have not been studied.

8 STUDY PROCEDURES AND VISIT SCHEDULE

8.1 CLINICAL PROCEDURES

The clinical procedures that will be conducted during this study related to the evaluation of population demographics, efficacy, immunogenicity, and safety are provided in Table 8.1-1 below. Refer to the Laboratory Manual for detailed instructions on how the assessments should be performed.

Table 8.1-1 Clinical Procedures: Demographics and Safety Evaluation

Assessment	Description
Demographics	Date of birth, age, sex, race and ethnicity
Medical history	Relevant medical history is defined as: any current medical condition ongoing at the time of signing ICF, or any recent or past medical history, which in the opinion of Investigator would potentially have an impact on subject's eligibility, study safety or immunogenicity outcomes. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during study participation, if it represents an exacerbation of an underlying disease/preexisting problem. Influenza vaccination history, and current/concomitant therapies should also be recorded.
Physical examination	Targeted physical examination as clinically indicated following the collection of medical history
Measurements	Body temperature (°F and °C) using axillary measurement. Body weight (kg)
Vaccination	Administration of one or two doses of Study Vaccine.
Blood sample	A volume of at least 3 mL of blood will be collected at each visit (Visit 1 and Exit Visit). Total volume of blood collected per subject is at least 6 mL. Blood will be centrifuged according to laboratory procedures and transported by courier from investigational sites to the central sample management laboratory.

Immunogenicity	Serum analyzed for the presence of binding antibodies specific to Study Vaccine by hemagglutination inhibition assay.
Virological test (if ILI case definition met)	<p>In the event of an influenza-like illness (ILI) between Visit 1 and Exit Visit nasal and throat swabs may be collected as follows:</p> <ul style="list-style-type: none"> • Nasal swab from the right nostril; • Nasal swab from the left nostril; and • Throat swab. <p>Nasal and throat swab specimens will be analyzed by the central analytical laboratory for laboratory confirmation of influenza A/B by reverse transcriptase polymerase chain reaction (RT-PCR).</p>

The timing and frequency of all clinical procedures are described in the [Schedule of Assessments](#). Refer to the Laboratory Manual for details about the collection, storage, handling and transportation of biological specimens.

8.2 RETENTION OF SAMPLES

Serum retention samples will be obtained at Visit 1 and Visit 2 or 3. Retention samples will be stored at [REDACTED], [REDACTED] in a secure facility under appropriate storage conditions for a maximum of 5 years after sign-off of the Clinical Study Report, after which retention samples will be destroyed. Retention samples may be used to perform additional serological analysis on the entire study population (or population subsets), using modified HI assays, or different assays types, including but not limited to viral microneutralization assays. Such additional assay analyses may be requested by regulatory agencies, or may be conducted by the Sponsor if there is a need for additional assay work to assist with the interpretation of the original study assay results, or to further characterize the immune response to influenza vaccination in the study population. Additionally, retention samples may be used to inform the development, performance, validation, or testing of new or modified assays to assess the serological impact of influenza vaccination. No form of genetic testing of the subject population will be performed at any time.

8.3 CONCOMITANT THERAPIES

All drugs and/or procedures (including any physician-prescribed dietary supplement or vitamin), currently being administered to a subject at the time of signing informed consent, and which continue to be taken in addition to the Study Vaccine during the Active Study Period, are regarded as concomitant therapies and must be documented as such in the eCRF. Concomitant medications that are being taken at the time of study enrollment should be initially recorded, and the reason for medication being taken should be recorded. At subsequent visits, any concomitant medications used during the active study period (from Day 1 until Exit Visit) should be recorded, and the reason for medication should be recorded. After the active study period, it is no longer necessary to routinely seek information on concomitant medications. However, if an SAE occurs after the Exit Visit, any medications

taken prior to and at the time of the SAE (whether or not related to the SAE) should be recorded.

8.4 VISIT SCHEDULE

The timing and frequency of the study visits are described in the [Schedule of Assessments](#). Time windows for all assessments are detailed in Table 8.4-1 below.

Table 8.4-1 Time Windows for Assessments

Visit/Procedure	Time window (relative to scheduled visit/procedure)
Screening (Day -7 to 1)	Not applicable.
Visit 1 (Day 1)	≤ 7 days after screening
Phone call (Day 3)	+ 2 days
Visit 2 (Day 29)	+ 4 days
Phone call (Day 3 after the 2 nd dose)	+ 2 days
Visit 3 (Day 29 after the 2 nd dose)	+ 4 days
Phone call (90 days after the last dose)	+ 7 days
Phone call (180 days after the last dose), End of Study	+ 7 days
ILI (if necessary)	Target for ≤ 3 days after onset of the symptoms meeting the case definition of an ILI.
Cellulitis-like reaction (if necessary)	Target for within 24 hours after onset of the symptoms meeting the cellulitis-like reaction criteria (or ≤ 3 days if on a weekend).

8.4.1 Screening

Parent(s) or legally appropriate representative must provide written informed consent before any study-specific assessments or procedures are performed. Written informed consent must be signed by the subject's parent or legally appropriate representative and the medically-qualified Investigator (MD or Doctor of Osteopathy) obtaining the consent. Written informed consent is not required for assessments or procedures performed according to standard of care (eg, for diagnosis or treatment); results from such assessments may be used in the determination of study eligibility.

A screening examination should be performed up to 7 days before the intended date of dosing (Day 1). If a potential subject was not enrolled into the study within 7 days of the first

screening visit, the potential subject may attend a second screening visit (for a maximum of two screening visits per subject). In the event that a potential subject is screened twice, a new subject number will be assigned and all screening assessments must be repeated at the second screening visit.

Subjects who complete all of these assessments and who fulfil the eligibility criteria (ie, eligible subjects) will be enrolled into the study. If the subject is not eligible for the study, the primary reason for screen failure must be entered in the eCRF.

Subjects will be recruited through generic advertisements or Institutional Review Board-approved study-specific advertisements. For those potential subjects interested in participating in the study, an appointment will be scheduled to allow informed consent to be obtained. Written informed consent can be provided by parents(s)/guardian(s) of subjects up to 1 week prior to the day of vaccination. The subject's age and influenza vaccination history will determine the dose and dosing regimen (a single vaccination or a two-vaccination regimen administered 28 days apart). The first vaccination will be administered at Visit 1 (Day 1) and the second vaccination, if scheduled will be administered at Visit 2 (Day 29+4).

8.4.2 Treatment Period

Visit 1 (Day 1) – Day of Vaccination (Either 1 or 2 Dose Schedule)

Informed Consent: A parent/guardian of the subject must provide written informed consent prior to any study-related procedures. Subjects with parent/guardian informed consent will be issued the next available unique subject number by IRT, including those who prove to be screen failures.

Prevaccination: The following assessments will be performed and documented in the source notes:

- A review of the subject's medical history, including concomitant medications, vaccination history (including influenza vaccination), and documentation of any relevant medical history;
- Targeted physical examination as clinically indicated following the collection of medical history;
- Subject's axillary temperature and body weight;
- A review of the subject's eligibility according to the Inclusion/Exclusion criteria
- Collection of at least 3 mL blood sample.

Subjects who complete the above assessments and who fulfill the inclusion/exclusion criteria will be eligible for randomization. Study vaccine will be assigned via IRT.

Vaccination: As per the US ACIP guidelines for seasonal influenza vaccination, the subject's age and influenza vaccination history determines the dose and dosing regimen (a single vaccination or a two-vaccination regimen administered 28 days apart). The first vaccination will be administered at Visit 1 (Day 1) and the second vaccination, if scheduled, will be administered at Visit 2 (Day 29 + 4). The Investigator/delegate will administer the study vaccine according to the randomization code into the deltoid region of the arm or into the anterolateral aspect of the thigh, by intramuscular injection. If vaccination into the arm is selected, the injection will be administered where possible into the contralateral arm to which the blood sample was drawn.

Subjects will receive the following dose depending upon their age at the time of administration of the first dose of Study Vaccine:

Cohort A	6 months through 35 months of age	0.25 mL
Cohort B	36 months through 59 months of age	0.5 mL

Postvaccination:

- Subjects will be observed for at least 30 minutes after vaccination for signs of an anaphylactic reaction. Appropriate medical treatment will be readily available in case of emergency.
- Parent(s)/guardian(s) will be issued with a digital thermometer and Local Reaction Measurement Card, and provided with electronic access to the 7-Day Diary (for recording solicited AEs), the Other Body Symptoms Diary (for recording unsolicited AEs), and the Medications Diary (for recording all concomitant medications). The 7-Day Diary will be completed on the day of vaccination and for the subsequent 6 days following vaccination (total of 7 days). The Other Body Symptoms Diary and the Medication AE Diary will be completed on the day of vaccination until the next study visit.
- Parent(s)/guardian(s) will be reminded how to measure axillary temperature and record their child's temperature at the same time each evening, in addition to completing the diaries.
- Parent(s)/guardian(s) will be instructed to contact the Investigator/delegate immediately if the subject experiences any signs or symptoms with grade 3 intensity.
- Parents will be educated on how to recognize the signs/symptoms of an ILI and will be instructed to contact the investigator/delegate immediately if the subject experiences any signs or symptoms of an ILI from Day 1 until the Study Exit Visit.
- An appointment will be made for each subject to return to the clinic 28 + 4 days after Visit 1 (Day 29 +4).

8.4.3 On-study Period

Diary Reminder Telephone Call (Day 3 + 2):

Sites will contact parent(s)/guardian(s) of subjects by telephone between Days 3 and 5 inclusive, to check that the electronic diaries are being completed daily, and to address any questions on how to complete them correctly.

Visit 2, Study Exit Visit (Single Dose Schedule) Day 29 + 4

Subjects who are scheduled to receive a single dose of study vaccine according to the previous immunization history, will exit the study at this visit.

The following will be undertaken and recorded at the Exit Visit:

- Review of the electronic diary entries;
- Assessment of the occurrence of any AEs, SAEs and AESIs;
- Targeted physical examination as clinically indicated;
- Collection of at least 3 mL blood sample.

OR

Visit 2, Second Vaccination (Two-Dose Schedule) Day 29 + 4

Subjects who are scheduled to receive 2 doses of study vaccine will require a second dose of study vaccine at this visit.

Prevaccination:

The following will be undertaken and recorded prior to administration of the second dose of study vaccine:

- Review of the electronic diary entries;
- Assessment of the occurrence of any AEs, SAEs and AESIs;
- Subject's ongoing eligibility will be reviewed;
- Targeted physical examination as clinically indicated;
- Subject's axillary temperature.

Vaccination:

Subjects will be injected following the same guidelines as for the first dose.

Subjects who are scheduled to receive 2 doses of study vaccine and who turn 36 months of age between the two study vaccinations will receive a second dose of 0.25 mL of study vaccine.

Postvaccination:

- Subjects will be observed for at least 30 minutes after vaccination for the signs of an anaphylactic reaction; Appropriate medical treatment will be readily available in case of emergency.
- Parent(s)/guardian(s) will be reminded to complete the 7-Day Diary entries for the day of the second vaccination and for the subsequent 6 days following vaccination (total of 7 days), and to continue recording unsolicited AEs in the Other Body Symptoms Diary and concomitant medications in the Medications Diary from the day of the second vaccination until the Study Exit Visit.
- Parent(s)/guardian(s) will be reminded on how to measure axillary temperature and record their child's temperature at the same time each evening, in addition to completing the diaries.
- Parent(s)/guardian(s) will be instructed to contact the Investigator/delegate immediately if the subject experiences any signs or symptoms with grade 3 intensity.
- Parent(s)/guardian(s) will be reminded on how to recognize the signs/symptoms of an ILI and will be instructed to contact the investigator/delegate immediately if the subject experiences any signs or symptoms of an ILI from Visit 2 until the Study Exit Visit.
- An appointment will be made for each subject to return 28 + 4 days post-Dose 2 for a Study Exit Visit (Day 29 + 4 days after the second vaccination).

Diary Reminder Telephone Call (Day 3 + 2 after the second vaccination):

Sites will contact parent(s)/guardian(s) of subjects by telephone between Days 3 and 5 inclusive after the second vaccination, to check that the diaries are being completed daily, and to address any questions on how to complete them correctly.

Visit 3, Study Exit Visit (Two-dose Schedule)

The Study Exit Visit for the Two-dose Schedule will occur 28 + 4 days after the administration of the second dose of Study Vaccine (Visit 2).

The following will be undertaken and recorded at this study visit:

- Review of the electronic diary entries;
- Assessment of the occurrence of any AEs, SAEs and AESIs;
- Targeted physical examination as clinically indicated;
- Collection of at least 3 mL blood sample.

Unscheduled Visit - Influenza-like Illness (ILI) Visit

Subjects reporting signs/symptoms of an ILI between Visit 1 and Study Exit Visit (Visit 2 or Visit 3) will be asked to attend an additional clinic visit within 72 hours of the symptoms meeting the case definition of an ILI, for confirmation of the ILI.

The criteria for an ILI are as follows:

- Elevated axillary temperature of $\geq 99.5^{\circ}\text{F}$ ($\geq 37.5^{\circ}\text{C}$) or a clear history of fever or chills; and
- At least one respiratory symptom, including sore throat, cough, wheezing, rhinorrhea/rhinitis; and
- At least one systemic symptom, including myalgia, headache, malaise and fatigue, diarrhea, nausea and/or vomiting, loss of appetite, and irritability.

To qualify as symptoms for the ILI case definition, symptoms should be either new, or for chronic symptoms, changed in severity or nature.

Influenza antiviral drugs (Symmetrel [amantadine], rimantadine, Tamiflu [oseltamivir] or Relenza [zanamivir]) should not be prescribed from any source until after the ILI assessment visit and the collection of respiratory specimens if indicated.

The site should perform an assessment to attempt to confirm a postvaccination ILI at the time of the ILI-assessment visit (the subject's temperature and clinical symptoms should be assessed). Additionally, the site may also confirm a postvaccination ILI through review of the AE diaries and/or illness history reported verbally by the subject at a time prior to the ILI visit. Information related to confirmation of a postvaccination ILI should be recorded in the subject's source notes.

Upon confirmation that the ILI case definition is met, the subject's temperature will be assessed and attempts will be made to diagnose influenza viral infection by obtaining nasal and throat swab specimens. These will be analyzed for laboratory confirmation of influenza A and/or B by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR).

Laboratory confirmation is more likely for specimens collected within approximately 3-4 days of illness onset, but nasal and throat swabs should be collected if the ILI assessment visit occurs up to 7 days after illness onset, to try to identify as many cases of laboratory confirmed influenza infection as possible. After 7 days following illness onset, the Investigator may choose whether to collect nasal and throat swabs, based on their clinical judgement of the potential value of testing specimens due to ongoing ILI symptoms.

Refer to the study-specific Nasal and Throat Swab Specimen Collection Instructions, for further details on collection, storage, handling and transportation of the nasal and throat swab specimens to the laboratory.

Unscheduled Visit – Cellulitis-like Reaction

Subjects reporting signs/symptoms of a Cellulitis-like Reaction between Day 1 and Study Exit Visit will be asked to attend an additional clinic visit within 24 hours (up to 3 days if on a weekend) of the symptoms meeting the definition of a cellulitis-like reaction.

The criteria for a Cellulitis-like Reaction are concurrent presence of all three of the following:

- Grade 3 injection site pain;
- Grade 3 injection site erythema;
- Grade 3 injection site induration.

Investigational site staff attending the subject will confirm if he or she meets or has met the cellulitis-like illness case definition postvaccination according to reported symptoms and, if applicable, will perform other clinical investigations as relevant according to routine clinical practice. Additionally, investigational site staff will assess for the presence of ulceration, abscess, or necrosis at the injection site, which will inform the application of study enrollment halting rules. In the event of a possible cellulitis-like reaction, sites should identify a local laboratory to perform any laboratory analyses to investigate, confirm, and manage any confirmed cellulitis-like reactions, and document any results in the source notes.

8.4.4 End of Study

Postvaccination Safety Follow-up Telephone Call (Day 90+7 and 180+7 after Last Vaccination)

Serious Adverse Event and AESI information will be collected for a total of 180 days (180+7 days) after administration of the last dose of study vaccine.

9 ADVERSE EVENTS

9.1 DEFINITIONS

9.1.1 Adverse Event

As per the ICH guideline (*Guidance for Industry, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting – ICH-E2A*), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

The period of observation for all adverse events extends from the time the parent or legally appropriate representative gives informed consent until 28 days after the last vaccination (Exit Visit). The period of observation for serious adverse events and adverse events of special interest extends from the time the parent or legally appropriate representative gives informed consent until the end of study (180 days after the last vaccination) – see [Section 9.4](#) (Observation Period for Adverse Events) for further details.

Adverse events may include:

- Exacerbation (ie, an increase in the frequency or severity) of a preexisting condition. Illness present before study entry should be recorded in the medical history section of the eCRF and only be reported as an AE if there is an increase in the frequency or severity of the condition during the study.
- A clinical event occurring after consent but before the investigational product administration.
- Intercurrent illnesses with an onset after administration of the investigational product.

Adverse events do not include:

- Events identified at screening that meet exclusion criteria
- Medical or surgical procedures (the condition that leads to the procedure is the AE)
- Situations where an untoward medical occurrence has not taken place. For example:
 - Planned hospitalizations due to pre-existing conditions, which have not worsened.
 - Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery).
 - Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (eg, chemotherapy).
- Overdose of Investigational Product or any concomitant therapy that does not result in any adverse signs or symptoms.

9.1.1.1 Solicited AEs

Solicited AEs are those events specifically sought for and recorded by the parent(s)/guardian(s) in the 7-Day Diary, entered on the day of vaccination and the subsequent 6 days.

Solicited Local Reactions (Vaccination Site)

Solicited local reactions are defined and graded as follows:

Table 9.1.1.1-1 Solicited Local Reactions

Reaction	Intensity Grading			
	None (0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain at the vaccination site	None	<i>For subjects less than 36 months of age at the time of the first dose of study vaccine:</i>		
		Minor reaction on touch	Cried/protected on touch	Cried when limb was moved/spontaneously painful
		<i>For subjects 36 months of age and older at the time of the first dose of study vaccine:</i>		
		Does not interfere with daily activities	Interferes with daily activities	Prevents daily activity
Redness at the vaccination site (erythema)*	Absent	< 10 mm	≥ 10 to ≤ 30 mm	> 30 mm
Induration/Swelling at the vaccination site*	Absent	< 10 mm	≥ 10 to ≤ 30 mm	> 30 mm

* Reaction to be measured in mm and recorded in the diary.

Solicited Systemic AEs

Solicited systemic AEs are defined and graded as follows:

Table 9.1.1.1-2 Solicited Systemic AEs

Solicited Systemic Adverse Event	Intensity Grading			
	None (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
<i>For all subjects:</i>				
Fever (Axillary)	<99.5°F (<37.5°C)	≥99.5 – <100.4°F (≥37.5 – <38.0°C)	≥100.4 – <101.3°F (≥38.0 – <38.5°C)	≥101.3°F (≥38.5°C)
Nausea and/or Vomiting	None	Adverse events easily tolerated by the subject, causing minimal discomfort and does not interfere with daily activities	Adverse event sufficiently discomforting to interfere with daily activities	Adverse event prevents normal everyday activities or requires significant medical intervention
Diarrhea				
<i>For subjects less than 36 months of age at the time of the first dose of study vaccine:</i>				
Loss of appetite	None	Adverse events easily tolerated by the subject, causing minimal discomfort and does not interfere with daily activities	Adverse event sufficiently discomforting to interfere with daily activities	Adverse event prevents normal everyday activities or requires significant medical intervention
Irritability				
<i>For subjects 36 months of age and older at the time of the first dose of study vaccine:</i>				
Malaise and fatigue	None	Adverse events easily tolerated by the subject, causing minimal discomfort and does not interfere with daily activities	Adverse event sufficiently discomforting to interfere with daily activities	Adverse event prevents normal everyday activities or requires significant medical intervention
Headache				
Myalgia				

9.1.1.2 *Unsolicited AEs*

Unsolicited AEs are all other AEs and will be recorded electronically on the Other Body Symptoms Diary or recorded by investigational site staff in the eCRF.

The intensity/severity of unsolicited AEs will be assessed by the subject's parent(s)/guardian(s) and graded as follows:

- Mild:** Symptoms are easily tolerated and do not interfere with normal, everyday activities;
- Moderate:** Discomfort enough to cause some interference with normal, everyday activities;
- Severe:** Symptoms that prevent normal, everyday activities.

9.1.2 Adverse Events of Special Interest

An AE of special interest (AESI) is an event considered to be potentially associated with a product or product class. Monitoring and reporting AESIs is an important aspect relating to characterizing the safety profile of a product during clinical development and post-authorization phases. As such, AESIs reported during clinical development, are considered as a medically important events, worthy of reporting as a serious adverse event.

The proposed AESIs selected for QIV are consistent with those that are considered as either identified or potential risk associated with pharmacological class of influenza vaccines. To generate additional information on these rare adverse events, the occurrence of the following AESIs during the study must be reported:

- Febrile convulsion
- Febrile delirium
- Bell's palsy
- Demyelinating disorders
- Encephalomyelitis
- Guillain-Barré syndrome
- Optic neuritis
- Transverse myelitis
- Thrombocytopenia
- Vasculitis

All AESIs must be reported as the same manner as an SAE (see [Section 9.6](#)). All AESIs will be recorded in the AE and SAE pages of the eCRF. An SAE Reporting Form must be submitted to Seqirus Product Safety. On the SAE page of the eCRF, there is a seriousness criteria checklist (see [Section 9.1.3](#)). For AESIs, the "medically significant" criteria must be selected on the SAE criteria checklist. Any other criteria may also be selected as applicable.

Additional clinical information regarding an AESI may be requested from the investigator to ascertain the diagnosis according to the available scientific literature or established case definition.

All AESIs will be reviewed for signal evaluation by Seqirus Safety and assessed for expedited reporting.

9.1.3 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- **Results in death** – The event must be the cause of death for the SAE to meet this serious criterion;
- **Is life-threatening** – The term “life-threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe;
- **Requires in-patient hospitalization or prolongation of existing hospitalization** – Seqirus considers “hospitalization or prolongation of existing hospitalization” for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs.
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly or birth defect.**
- **Is medically significant** – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is judged by a physician to potentially jeopardize the subject or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion.
- **Is the suspected transmission of an infectious agent via a medicinal product.**

Adverse events that do not fall into the above categories are defined as nonserious AEs.

9.2 SEVERITY OF ADVERSE EVENTS

The severity of each AE (ie, nonserious and serious AEs) is to be assessed as follows:

Severity	Definition
Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM) Severity Intensity Scale for Adverse Event Terminology

9.3 CAUSALITY OF ADVERSE EVENTS

The causal relationship of an AE to the Study Vaccine must always be assessed by the Investigator. All solicited local AEs will be assessed as related to the Study Vaccine. All other AEs will be classified as either **related** or **not related** to the Study Vaccine. If a causality assessment is not provided for an AE (including an SAE), the AE will be considered related to the Study Vaccine.

The degree of certainty with which an AE is attributed to the Study Vaccine or an alternative cause (eg, natural history of the underlying disease, concomitant therapy) will be determined by how well the event can be understood in terms of:

- Known pharmacology of the Study Vaccine;
- Clinically and/or pathophysiologically plausible context;
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related (eg, headache, facial flushing, pallor);
- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with the Study Vaccine, drug withdrawal or reproduced on rechallenge).

9.4 OBSERVATION PERIOD FOR ADVERSE EVENTS

The observation period for AE reporting in an individual subject will start at the time of giving written informed consent for participation in the current study and finish at 28 days after the last vaccination (the Exit Visit).

The observation period for SAE and AESI reporting in an individual subject will start at the time of giving written informed consent for participation in the current study and finish 180 days after the last vaccination.

If the Investigator becomes aware of an SAE or AESI that has started after the observation period has finished, and the event is considered by the Investigator to be causally related to the Study Vaccine, then this must also be reported to Seqirus Safety - see [Section 9.6](#) (Serious Adverse Event Reporting).

9.5 ADVERSE EVENT REPORTING

9.5.1 Adverse Events

At each clinical evaluation, the investigator (or delegate) will determine whether any AEs have occurred. AEs will be recorded in the AE page of the eCRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs and symptoms.

If, during the study period, a subject presents with a relevant medical history that was not noted at the time of study entry, the condition should be retrospectively recorded in the Medical History section of the eCRF.

For AE reporting, the study period is defined as that time period from the signature of the informed consent form through the Exit Visit. Therefore, events that occur before the initial screening visit will be recorded in the medical history and events that occur after the signing of the informed consent form will be recorded as an AE.

9.5.2 Adverse Events of Special Interest

All AESIs must be reported as the same manner as an SAE (see [Section 9.6](#))

9.6 SERIOUS ADVERSE EVENT REPORTING

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the AE/SAE page of the eCRF. If entry into the eCRF is not possible (eg, because of an internet access problem), a paper SAE data collection form must be completed.

All SAEs that occur during the observation period for SAEs (from the time of Informed Consent to Day 180, see section 9.4), whether or not considered causally related to Study Vaccine, MUST BE REPORTED IMMEDIATELY (within 24 hours of becoming aware of the event) to Seqirus. Adverse events occurring in the period between the time of provision of written informed consent and the first exposure to the Study Vaccine that meet one or more of the seriousness criteria for AEs must be reported to Seqirus Safety in the same manner as other SAEs and will be included in the clinical study database.

Any SAE that occurs after the Day 180 Follow-up Phone call that is considered to be causally related to the investigational product must be **reported immediately (ie, within 24 hours of the Investigator becoming aware of the event) to Seqirus.**

Prompt notification is essential so that regulatory requirements for SAE reporting and ethical obligations to the subjects involved in the study can be met.

Guidance for reporting SAEs will be provided to study sites before the study starts. Details for reporting of SAEs will be described in the SAE reporting plan and eCRF completion guidelines.

Seqirus Safety contact details for SAE reporting:

Facsimile (US):	1-866-546-4953
Email:	ProductSafety@biocsl.com.au

9.6.1 Requirements for Immediate Reporting of Serious Adverse Events

For SAEs occurring during the study the Investigator/delegate will complete the AE/SAE page and other relevant pages of the eCRF. The Investigator/delegate must include all relevant information regarding the event.

The minimum reporting requirements for immediate reporting of SAEs include:

- Identifiable subject.
- Suspected medicinal product and / or procedure.
- Event term.
- Identifiable reporting source.

If the minimum requirements for reporting are fulfilled, the Investigator should not wait to receive additional information to fully document the event before notifying Seqirus.

In addition, the Investigator must:

- Report all SAEs to the relevant IRB / IEC within the timeframe specified by the IRB / IEC.
- Submit follow-up reports to Seqirus Safety until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
- Ensure that the causality assessment for all SAEs is entered in the eCRF.

When submitting SAE reports and any other related reports (eg, discharge summaries) to Seqirus, subjects should be identified only by their subject number and study number. The investigator should not include the subject's name, date of birth, or address.

In cases of death, the investigator should supply Seqirus and the IRB (as applicable) with any additional information as it becomes available (eg, autopsy reports and detailed medical reports).

The procedure to be followed if an ongoing AE becomes an SAE after the end of the observation period for AEs is described in [Section 9.9](#) (Follow-up of Adverse Events).

9.7 OTHER SIGNIFICANT EVENT REPORTING - ENROLLMENT HALTING RULES

An independent Data Safety Monitoring Board (DSMB) will monitor subject safety during the study. The DSMB will comprise clinical study experts with experience in vaccine studies and safety assessment. The DSMB will provide recommendations for stopping or continuing the study based on the assessment of study safety data according to processes defined in the study protocol and the DSMB Charter.

Enrolment into the study and study vaccination will be halted for DSMB review/ recommendation for continuation if during the 7 days after vaccination (Day 1 to Day 7) any of the following occur:

- One or more subject experiences an AE that is serious, unexpected, and is assessed as related to Study Vaccine;
- One or more subject experiences an AE that is life-threatening or causes death;
- One or more subject experiences a serious febrile AE, defined as any AE meeting seriousness criteria that is also associated with a fever of $\geq 101.3^{\circ}\text{F}$ / $\geq 38.5^{\circ}\text{C}$ (axillary).
- One or more of the subjects experiences a severe (grade 3)
 - allergic reaction (eg, hives, angioedema, allergic asthma, systemic anaphylaxis);
 - Vaccine-related injection site ulceration, abscess, or necrosis;

Additionally, enrolment into the study and study vaccination will be halted pending review by the DSMB if during Day 1 to Day 7, the following defined halting rule criteria are met in either study cohort (6 months through 35 months or 36 months through 59 months):

- $\geq 5\%$ of subjects enrolled to date, with concurrent grade 3 pain, erythema, and induration (a cellulitis-like reaction) that is assessed as related to Study Vaccine.

(Note: If the total number of subjects enrolled to date is less than 60, a minimum of 3 subjects experiencing a concurrent severe vaccine-associated pain, erythema or induration will be needed to halt further enrolment);

- $\geq 5\%$ of subjects enrolled to date experience a fever of $\geq 101.3^{\circ}\text{F}$ / $\geq 38.5^{\circ}\text{C}$ (axillary) that is assessed as related to Study Vaccine.

(Note: if the total number of subjects enrolled to date is less than 60, a minimum of 3 subjects is required to trigger the halt).

In addition, the DSMB chair will be immediately notified of any SAE, regardless of causality or expectedness assessment, occurring during Day 1 to Day 7. The DSMB chair will then make a determination regarding the necessity of a DSMB meeting and/or study halt in response to these events.

Any decision to terminate the study will be made by Seqirus in consultation with the DSMB, and the study investigators.

9.7.1 Overdose

Details (ie, volume, location of injection) of overdose of the investigational product or any concomitant therapy must be recorded in the eCRF. Any overdose that is considered by the Investigator to be medically significant must be reported as an SAE, see [Section 9.6](#) (Serious Adverse Event Reporting).

9.7.2 Pregnancy and Lactation

Not applicable.

9.8 IRB / IEC REPORTING REQUIREMENTS

The time frame within which an IRB must be notified of deaths and investigational product-related unexpected SAEs is stipulated by each IRB. It is the Investigator's responsibility to comply with the requirements for IRB notification. Seqirus will provide Investigators with all details of all SAEs reported to regulatory authorities.

9.9 FOLLOW-UP OF ADVERSE EVENTS

Every effort should be made to follow-up subjects who continue to experience an AE or an SAE on completion of the study until either the AE resolves or stabilizes, whichever is sooner. All follow-up information (and attempted follow-up contacts) should be documented in the subject's medical records. Details of SAE follow-up should also be submitted to Seqirus Safety.

10 ASSESSMENTS

10.1 SUBJECT CHARACTERISTICS

Subject characteristics to be evaluated will include:

- Demographic data (eg, date of birth, age, sex, race, ethnicity)
- Medical history and documentation of relevant medical history, defined as 1) any current medical condition ongoing at the time of signing ICF; 2) any recent or past medical history, which in the opinion of Investigator would potentially have an impact on subject's eligibility, study safety or immunogenicity outcomes. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during study participation, if it represents an exacerbation of an underlying disease/preexisting problem.
- Influenza vaccination history
- Body weight and axillary temperature
- Current/concomitant therapies.

10.2 EFFICACY (IMMUNOGENICITY) ASSESSMENTS

Efficacy assessment involves the assessment of immunogenicity on the basis of HI antibody titer to each strain, performed on serum specimens taken at Day 1 (Visit 1) and at the Study Exit Visit (Visit 2 – single dose schedule or Visit 3 – two-dose schedule).

Immunogenicity will be expressed as:

- *HI antibody titer for each strain:* All analyses involving HI antibody titer (namely GMT within a treatment group) will be based on the log scale and the resultant summary statistic back-transformed to derived GMT;
- *Seroconversion:* For each strain the subjects will be classified as 'seroconverted' if either they have a prevaccination HI antibody titer < 1:10 and a postvaccination HI antibody titer \geq 1:40 or a prevaccination HI antibody titer \geq 1:10 and a \geq 4-fold increase in postvaccination HI antibody titer. Otherwise they will be classified as 'not seroconverted';
- *Seroprotection:* For each strain a subject will be classified as 'seroprotected' if their HI antibody titer \geq 1:40 at Days 1 and the Study Exit Visit. If they do not have both antibody titers \geq 1:40 they will be classified as 'not seroprotected';
- *Fold increase:* For each strain the fold increase for each subject will be calculated by taking the ratio of the postvaccination antibody titer over the prevaccination antibody titer;
- Covariate adjusted analyses will be performed as outlined in the Statistical Analysis Plan (SAP)

10.3 SAFETY ASSESSMENTS

Safety will be assessed through solicited local reactions, solicited systemic AEs, unsolicited AEs and SAEs.

Type, frequency and intensity of solicited local reactions through to Day 7 (Day 1, 2, 3, 4, 5, 6, 7) following each study vaccination dose. These include pain, induration/swelling, and erythema/redness.

Frequency of cellulitis-like reaction for 28 days following vaccination. Cellulitis-like reaction is defined as the concurrent presence of grade 3 injection site pain, erythema/redness and induration/swelling.

Type, frequency, duration and intensity of solicited systemic AEs through to Day 7 (Day 1, 2, 3, 4, 5, 6, 7) following each study vaccination dose. These include headache, malaise and fatigue, myalgia, fever, diarrhea, and nausea and/or vomiting for children 36 months through 59 months of age, and fever, diarrhea, nausea and/or vomiting, loss of appetite, and irritability for children 6 months through 35 months of age.

Frequency of antipyretic use in the 7 days after each vaccination dose.

Type, frequency, duration and intensity of unsolicited AEs for at least 28 days following each study vaccination dose.

Frequency of SAEs and AESIs for at least 180 days following vaccination.

10.4 PHARMACOKINETIC AND PHARMACODYNAMICS

Not applicable.

10.4.1 Pharmacokinetic Analyses

Not applicable.

10.4.2 Pharmacodynamic Analyses

Not applicable.

10.4.3 Pharmacokinetic / Pharmacodynamic Relationships

Not applicable.

10.5 OTHER ASSESSMENTS

Not applicable.

11 STATISTICS

11.1 SAMPLE SIZE ESTIMATION

Statistical considerations for sample size calculations:

Seqirus QIV will be tested against a US licensed comparator QIV. The treatment randomization ratio is 3:1 (Seqirus QIV: Comparator QIV). This study is designed to achieve at least 80% power to demonstrate noninferiority for all of the 8 co-primary endpoints, seroconversion rates for 4 strains, GMT for 4 strains using a one-sided alpha of 0.025 for each comparison. No adjustment for multiple endpoints was made. For comparisons of SCR a noninferiority margin of 10% (Seqirus QIV - Comparator QIV) will be employed. It is assumed that the SCR for all strains for QIV is 50% and that there is no difference between Seqirus QIV and Comparator QIV.

For comparison of GMT ratio a noninferiority margin of 1.5 (Comparator QIV/ Seqirus QIV, equivalent to a difference on the log scale of 0.405465108) will be employed. It is assumed that there is no difference between Seqirus QIV and Comparator QIV (ie, a ratio of 1, difference on the log scale of 0) and that the standard deviation of log (titer) is 1.4.

Under these assumptions and with n evaluable = 1500 in the Seqirus QIV group and 500 in the Comparator QIV the power for 4 GMT ratio endpoints is 99.95% and the power for 4 SCR endpoints is 89.70%. The overall global power of the 8 endpoints is then $89.7\% \times 99.95\% = 89.66\%$.

This provides a total N evaluable = 2000 (with 10% dropouts N=2222). Sample size calculations were performed using SAS v9.3 and PASS v12.0.02.

[Table 11.1-1](#) summarises the list of all primary endpoints with strains, the planned noninferiority margin and underlying assumptions used for the sample size computations.

Table 11.1-1: Summary of Assumptions Used for Sample Size Calculations

	H1N1	H3N2	B strains
Test significance level, alpha (1-sided)	2.50%	2.50%	2.50%
Noninferiority Margin for the SCR comparison (%)	10	10	10
Assumed true SCR	50%	50%	50%
Power for SCR comparison tests for each strain (%)	97.32%	97.32%	97.32%
Global Power for 4 SCR Endpoints	89.70%		
Noninferiority Margin for the GMT ratio	1.5	1.5	1.5
Common Standard Deviation of $\log_e(\text{titre})$	1.4	1.4	1.4
Power for GMT ratio tests for each strain (%)	99.99%	99.99%	99.99%
Global Power for 4 GMT ratio Endpoints	99.95%		
Global Power for 8 Co-primary Endpoints	89.66%		

11.2 DESCRIPTION OF ANALYSIS DATASETS

There will be four analysis populations defined for the study analyses. These are defined in more detail in the SAP.

11.2.1 Full Analysis Set

The Full Analysis Set (FAS) will comprise all subjects who provide informed consent and who were randomized to treatment. Screening failures will not be included in the FAS. However, the number of screening failures will be summarized in the disposition tables and all screening failures will be listed.

The FAS will be used to produce summaries and listings of subject characteristics.

11.2.2 Safety Population

The Safety Population will comprise all subjects in the FAS who received at least one dose or partial dose of Study Vaccine and have provided any evaluable follow-up safety data. The safety population will be used to produce summaries and listings of all safety data.

Follow-up safety data is defined as any safety information that is recorded for a subject in a Study Diary or in the subject's medical notes.

11.2.3 Evaluable Population – Immunogenicity Analysis

The Evaluable Population for immunogenicity analyses will comprise all subjects in the FAS who:

- receive vaccine at Visit 1;

- provided serology specimens which provided valid serology assay results from both Visit 1 and the Study Exit Visit (Visit 2 or 3);
- did not experience a laboratory-confirmed influenza illness between Visit 1 and Study Exit Visit (Visit 2 or 3); and
- did not receive any prohibited medication during the study that is medically assessed to potentially impact immunogenicity results.

11.2.4 Per-Protocol Population

The Per-Protocol Population (PPP) will comprise all subjects in the Evaluable Population who do not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results.

The Per Protocol Population will be the primary population of interest for the primary immunogenicity analysis and a supporting analysis will be performed using the Evaluable Population.

Membership of the PPP will be determined prior to unblinding the study.

11.3 STATISTICAL ANALYSES AND METHODS

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan, which will be finalized before the database is locked.

11.3.1 Subject Disposition and Characteristics

11.3.1.1 Subject Disposition

The number of subjects who were screened, enrolled into the study, and completed the study, will be presented in summary tables by treatment group, by age cohort and overall. The number and percentage of subjects in each population will be presented in summary tables by treatment group, by age cohort and overall. The number in the full analysis set will be used as the denominator. The primary reason for discontinuing the study product or withdrawing a subject from the study will be summarised by treatment group, by age cohort and overall. All data will be listed by subject.

11.3.1.2 Subject Characteristics

At a minimum, subject characteristics will be presented in summary tables by treatment group, by age cohort and overall. Continuous data will be summarized by descriptive statistics (n, mean, median, minimum, maximum and standard deviation) and categorical data will be summarized by contingency tables (frequency and percentage). Age will be described as both a continuous and a discrete variable. All data will be listed by subject.

11.3.2 Study Analyses

11.3.2.1 Primary Analysis

Primary Objective

The primary objective is to demonstrate that vaccination with Seqirus QIV elicits an immune response that is not inferior to the US-licensed comparator QIV containing the same virus strains as Seqirus QIV among a pediatric population 6 months through 59 months of age.

Primary Endpoints:

Co-primary immunogenicity endpoints of geometric mean titer (GMT) and seroconversion rate for each virus strain contained in the vaccine will be assessed. The rate of seroconversion is defined as the percentage of subjects with either a prevaccination hemagglutinin inhibition (HI) titer < 1:10 and a postvaccination HI titer \geq 1:40 or a prevaccination titer \geq 1:10 and a \geq 4-fold increase in postvaccination titer.

The noninferiority of Seqirus QIV compared to the US licensed comparator QIV will be assessed by the 8 co-primary endpoints of GMT and seroconversion rate.

In line with the FDA Guidance on seasonal inactivated influenza vaccines (*Guidance for Industry Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines 2007*), Seqirus QIV will be considered to be noninferior to the US licensed comparator QIV for each strain if:

- The upper bound of the two-sided 95% confidence interval (CI) on the ratio of the GMTs does not exceed 1.5. The GMT ratio will be calculated by $\text{GMT}_{\text{Comparator QIV}} / \text{GMT}_{\text{Seqirus QIV}}$
- The upper bound of the two-sided 95% CI on the difference between the seroconversion rates does not exceed 10%. The difference in seroconversion rate will be calculated by $(\text{Seroconversion}_{\text{Comparator QIV}} - \text{Seroconversion}_{\text{Seqirus QIV}})$.

To determine the GMT ratio (adjusted analysis) a general linear model (GLM) will be fitted on log transformed postvaccination HI titer (titer) as the outcome variable and with inclusion of covariates such as vaccine treatment, prevaccination HI titer, age stratum, sex, vaccination history, age-by-vaccine interaction and study site.

From the model an adjusted difference in least-square means (on the log scale) will be produced with 95% confidence limits. The estimated difference and the confidence limits will be back transformed to obtain an *adjusted GMT ratio* with 95% confidence limits. Each of the four strains will be analyzed separately. The adjusted GMT ratio will be the result for which the noninferiority assessment will be based on. The measure of the *unadjusted GMT ratio* based on postvaccination GMTs only will also be presented.

If all 8 co-primary endpoints result in a conclusion of noninferiority then overall noninferiority of Seqirus QIV compared to the US licensed comparator QIV will be concluded.

This assessment will be conducted overall (the primary endpoint).

In mathematical notation the statistical hypotheses to be tested for the primary immunogenicity analysis corresponds to:

$H_0: R_i > 1.5$, for any strain
 $H_a: R_i \leq 1.5$, for all strain

and

$H_0: D_i > 10$, for any strain
 $H_a: D_i \leq 10$, for all strain

where R_i is any of the 4 strain-specific post immunogenicity dose GMT ratios:

- (US licensed comparator QIV) / Seqirus QIV for B/Yamagata strain
- (US licensed comparator QIV) / Seqirus QIV for B/Victoria strain
- (US licensed comparator QIV) / Seqirus QIV for A/H1N1 strain
- (US licensed comparator QIV) / Seqirus QIV for A/H3N2 strain

and D_i is the 4 strain-specific post-dose SCR difference, namely:

- (US licensed comparator QIV) - Seqirus QIV for B/Yamagata strain
- (US licensed comparator QIV) - Seqirus QIV for B/Victoria strain
- (US licensed comparator QIV) - Seqirus QIV for A/H1N1 strain
- (US licensed comparator QIV) - Seqirus QIV for A/H3N2 strain.

No adjustment will be made for multiple comparisons.

11.3.2.2 Secondary Analyses

Secondary Objectives:

The secondary objectives of the study are:

1. To assess the safety and tolerability of Seqirus QIV, in two age strata: 6 months through 35 months and, 36 months through 59 months of age, as well as overall.

2. To characterize the immunogenicity of Seqirus QIV and the US-licensed comparator QIV in two age strata: 6 months through 35 months and, 36 months through 59 months, as well as overall.

Secondary Endpoints:

Secondary safety endpoints:

AEs will be monitored after vaccination as per the following;

- Frequency and severity of solicited local adverse reactions and systemic adverse events (AEs) for 7 days (ie, day of vaccination and 6 subsequent days) after each vaccination dose;
- Frequency of cellulitis-like reaction for at least 28 days after each vaccination dose;
- Frequency and severity of unsolicited AEs for at least 28 days (ie, day of vaccination and 27 subsequent days) after each vaccination dose;
- Frequency of serious adverse events (SAEs) for 180 days after the last vaccination dose.

For all solicited AEs the following summaries will be presented by treatment group overall and by age stratum:

- The number and percentage of subjects reporting at least one occurrence of each type of adverse event will be presented with 95% CIs.
- The number and percentage of subjects experiencing at least one local reaction will be presented with 95% CIs.
- The number and percentage of subjects experiencing at least one systemic adverse event will be presented with 95% CIs.

For each of these summaries the relative risk and 95% CIs will be presented for Seqirus QIV/Comparator QIV.

All summaries will be presented overall and by maximum intensity. Analyses will be repeated by sex and by race/ethnicity where specified.

Unsolicited AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number (and percentage) of subjects experiencing at least one event (ie, the incidence) of unsolicited AEs will be summarized by body system overall and by maximum intensity. All summaries will be presented by treatment group overall and by age stratum. Analyses will be repeated by sex and by race/ethnicity where specified.

Summaries will be presented for:

- Any AEs
- Any AEs by maximum severity

- Any AEs by relationship to Study Vaccine
- Any SAEs
- Any SAEs by maximum severity
- Any SAEs by relationship to Study Vaccine
- Any discontinuations due to AEs
- Any discontinuations due to AEs related to Study Vaccine
- Any discontinuations due to SAEs
- Any discontinuations due to SAEs related to Study Vaccine
- Any deaths

If sufficient numbers of cases of AEs occur, more formal statistical analyses of event rates, duration or intensity may be conducted.

Secondary immunogenicity endpoints

The humoral immune response will be assessed in terms of HI antibodies for both Seqirus QIV and the QIV comparator. Serum HI antibody titers against the 4 influenza vaccine strains will be used to calculate:

- GMTs: Geometric mean of HI titers prevaccination (Day 1) and postvaccination (Study Exit Visit);
- SCRs: Percentage of subjects with either a prevaccination HI titer $< 1:10$ and a postvaccination HI titer $\geq 1:40$ or a prevaccination titer $\geq 1:10$ and a ≥ 4 -fold increase in postvaccination titer;
- The percentage of subjects with a titer ≥ 40 (seroprotection rates) at Day 1 and at Study Exit Visit;
- Geometric mean fold increase (GMFI)*: Geometric mean fold titer rise from Day 1 to Study Exit Visit.

**GMFI in antibody titer is defined as the geometric mean of the fold increase of postvaccination HI antibody titer over the prevaccination HI antibody titer.*

For each treatment group (each age stratum as well as overall) for each strain summary tables will be presented for GMT (mean and 95% CIs), seroprotection rates (number and percentage of subjects) at Day 1 and Study Exit Visit, Day 28, SCR (number and percentage of subjects at Study Exit Visit) and GMFI (mean and 95% CIs).

The distribution of antibody titers 6 months through 35 months of age, 36 months through 59 months of age, as well as overall will be displayed graphically using reverse cumulative distribution (RCD) curves. Separate RCD curves following the first and second vaccinations will also be displayed.

Further specifics of the statistical analyses will be detailed in the SAP.

Exploratory Objective:

The exploratory objective of the study is:

- To assess the frequency of antipyretic use in the first 7 days postvaccination in two age strata: 6 months through to 35 months, and 36 months through 59 months, as well as overall according to treatment group.

Exploratory endpoint

Frequency of antipyretic use in the 7 days after each vaccination dose

The frequency of antipyretics use in the 7 days after each vaccination dose will be summarised according to age and treatment group.

11.3.3 Safety Analyses

See [Section 11.3.2.2](#).

11.3.4 Pharmacokinetics and Pharmacodynamic Data

Not applicable.

11.3.5 Other Analyses

Not applicable.

11.3.6 Interim Analysis

An interim analysis will be conducted on data generated from Visit 1 through to the Exit Visit, once all subjects have completed all immunogenicity assessments and all solicited and unsolicited adverse event reporting.

12 QUALITY ASSURANCE

The study may be subject to audits by Seqirus, an authorized representative(s) of Seqirus and may also be subject to inspections by an authorized regulatory authority (eg, US Food and Drug Administration [FDA]). Regulatory authorities may request access to all study documentation, including source documents for inspection and copying, in keeping with local regulations. Seqirus or an authorized representative will notify the Investigator of planned audits and/or Regulatory Authority inspections if prior notification is received.

If the Investigator is contacted and/or notified of an inspection by US FDA, they should immediately notify Seqirus or an authorized representative.

In the event of an audit, all pertinent study-related documentation must be made available to the auditor(s). If an audit or inspection occurs, the investigator at each study site will permit the auditor / inspector direct access to all relevant documents and allocate their time as well as the time of relevant staff to discuss the findings and any relevant issues.

13 REGULATORY AND ETHICS CONSIDERATIONS

13.1 REGULATORY CONSIDERATIONS

Seqirus or its agents will submit the appropriate documents to the local regulatory agencies and will await approval as applicable to local regulatory requirements before study start.

This study will be conducted under an FDA Investigational New Drug application, and documented in accordance with the applicable regulatory guidelines and requirements.

The procedures set out in this study protocol are designed to ensure that Seqirus and the investigator abide by the principles of the current ICH GCP guideline on the conduct, evaluation and documentation of this study, as described in ICH Topic E6 (Guideline for GCP). The study will also be carried out according to all applicable international and national regulatory requirements.

This study will be conducted and documented in accordance with the following (nonexhaustive) list of guidelines and regulations:

1. The Declaration of Helsinki (June 1964), as modified by the 64th General Assembly, Fortaleza, Brazil (2013).
2. ICH Topic E2A. Guidance for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.
3. ICH Topic E3. Note for Guidance on Structure and Content of Clinical Study Reports.
4. ICH Topic E6 (R1). Guideline for Good Clinical Practice.
5. ICH Topic E9. Statistical Principles for Clinical Trials.
6. Code of Federal Regulations (21 CFR) Part 11 – Electronic Records; Electronic Signatures.

7. Code of Federal Regulations (21 CFR) Part 50 – Protection of Human Subjects.
8. Code of Federal Regulations (21 CFR) Part 54 – Financial Disclosure by Clinical Investigators.
9. Code of Federal Regulations (21 CFR) Part 56 – Institutional Review Boards
10. Code of Federal Regulations (21 CFR) Part 312 – Investigational New Drug Application.
11. Center for Biologics Evaluation and Research (CBER). Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical Trial Data and Monitoring Committees. March 2006.
12. Center for Biologics Evaluation and Research (CBER). Guidance for Industry Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines 2007.
13. Center for Biologics Evaluation and Research (CBER). Guidance for Industry: E2F Development Safety Update Report 2011.
14. EU Clinical Trial Directive 2001/20/EC.
15. EU GCP Directive 2005/28/EC.
16. Committee for Proprietary Medicinal Products. Note for Guidance on Harmonisation of Requirements for Influenza Vaccines. 1997.
17. The Medicines for Human Use (Clinical Trials) Regulations 2004.

13.2 INSTITUTIONAL REVIEW BOARD

The Investigator must submit the protocol, informed consent forms (ICFs), and any other written information to be provided to parent(s)/guardian(s) and subjects for review by an authorized and properly constituted IRB (according to local guidelines). Written approval must be received from the IRB before commencement of the study and should state the study protocol and other relevant documents by title, number, and version date.

Written notification of the composition and occupation of the members of the IRB is also required by Seqirus. Should the IRB be unwilling to provide this information, a letter stating that the committee is constituted in accordance with the applicable guidance would be required.

13.3 SUBJECT INFORMATION AND INFORMED CONSENT

An Investigator (medically qualified as an MD or DO only) will explain the nature, purpose and risks of the study and provide the parent (or legally acceptable representative) with a copy of the informed consent form. Subjects and parents (or legally acceptable representative) must be given ample opportunity to consider the contents of the information provided and to ask questions before deciding whether to participate.

Consent forms will be in a language fully comprehensible to the prospective subject's parent (or legally acceptable representative). Informed consent will be documented by the use of a

written consent form approved by the IRB and signed by the parent (or legally acceptable representative) and the Investigator obtaining the consent.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and ICH/GCP and will also comply with local regulations. Consent must be documented by the parent(s) (or legally acceptable representative) dated signature. The signature confirms the consent is based on information that has been understood. Each parent's (or legally acceptable representative) signed informed consent form must be kept on file by the Investigator.

Should there be any amendments to the protocol that would directly affect the subject's participation in the study (eg, a change in any procedure), the ICF will be amended to incorporate this modification. The parent (or legally acceptable representative) must be informed of the change and they must sign the amended ICF indicating that they re-consent to continue participation in the study.

13.4 SUBJECT IDENTIFICATION AND CONFIDENTIALITY

All subject names and contact details will be kept confidential. Subjects will be identified throughout documentation and evaluation by the number allotted to them during the study. Each subject will be told that all study findings will be handled in the strictest confidence.

The Investigator at the study site will be responsible for retaining sufficient information about each subject (eg, name, address, phone number and identity in the study) so that regulatory agencies or Seqirus may access this information should the need arise. These records should be retained in a confidential manner as long as legally mandated according to local requirements.

Subject medical records pertaining to the study may be inspected / audited at any time by Seqirus employees or their duly authorized representatives, a regulatory authority or the IRB. All records accessed will be strictly confidential. Consent to participate in the study includes consent to these inspections / audits and this information is communicated in the subject informed consent information.

13.5 INDEMNITY AND COMPENSATION

It is Seqirus policy that persons who participate in Seqirus' clinical studies should be no worse off for their having been involved in the study. These persons include the subjects, the Investigator, the study site and the IRB.

Seqirus has secured insurance to cover its obligations under both the Indemnity and the Compensation guidelines for injury to subjects involved in the study.

Other details regarding subject compensation and the obligations of the investigator / Seqirus are provided in the Clinical Trial Agreement and Informed Consent Form for the study; see [Section 14.1](#) (Clinical Trial Agreement).

14 ADMINISTRATIVE CONSIDERATIONS

14.1 CLINICAL TRIAL AGREEMENT

This study will be conducted under a Clinical Trial Agreement between the Contract Research Organization (the “CRO”) commissioned by Seqirus (“the Sponsor”) and the institution(s) representing the investigational study site(s) (the “Authority”). Financial support to the investigational site(s) will be detailed in the Clinical Trial Agreement. The Clinical Trial Agreement must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of the Investigator and the CRO, and will form the contractual basis under which the clinical study will be conducted.

14.2 CLINICAL STUDY REGISTRATION AND RESULTS DISCLOSURE

Seqirus will provide the relevant study protocol information in public database(s) before or at commencement of the study. Seqirus may also provide study information for inclusion in national registries according to local regulatory requirements.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record.

14.3 IMPLEMENTATION OF THE PROTOCOL / PROTOCOL AMENDMENT(S)

With the exception of medical emergencies, no changes or deviations in the conduct of the signed protocol will be permitted without documented approval of Seqirus and the IRB. In the event of a medical emergency, the Investigator at the study site will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the Seqirus Medical Monitor and the IRB.

Modifications to the protocol that may affect subject safety or the way the study is to be conducted will be documented in a protocol amendment, which must be approved by the IRB.

Administrative changes to the protocol, defined as minor corrections and/or clarifications that have no effect on the way the study is to be conducted, will not require IRB approval, but will be submitted to the IRB for their information.

14.4 PROTOCOL DEVIATIONS

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. As a result of deviation, corrective action should be developed by the site and implemented promptly.

These practices are consistent with ICH Good Clinical Practice (GCP ICH E6):

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2 and 4.5.3

5.1 Quality Assurance and Quality Control, section 5.1.1

5.20 Noncompliance, sections 5.20.1 and 5.20.2

ICH GCP does permit deviations from the protocol by the Investigator when necessary to eliminate immediate hazards to the subjects, but this should not be related to the inclusion and exclusion criteria. No prospective protocol deviations (waivers) will be granted during the study.

All instances where the requirements of the study protocol were not complied with will be recorded and tracked. Protocol deviations should be reported to the IRB in accordance with their guidelines. Additionally, any major protocol deviations should be reported to Seqirus (or delegate) as soon as possible.

Major protocol deviations are deviations that could significantly affect the subject's safety, rights, or welfare and/or significantly impact the completeness, accuracy and reliability of the study data. Examples of major protocol deviations include enrolling subjects in violation of inclusion/exclusion criteria defined in the protocol, or failing to collect prevaccination or postvaccination blood samples.

Minor protocol deviations are deviations that do not significantly affect the subject's safety, rights, or welfare and/or significantly impact the completeness, accuracy and reliability of the study data. Examples of minor protocol deviations include a blood sample not being drawn at an interval specified by the Study Protocol.

Please refer to the Protocol Deviation Plan for further definition and guidance.

14.5 DOCUMENTATION AND RECORD KEEPING

14.5.1 Data Collection

The Investigator (or delegate) will maintain individual records for each subject. These records should include verification of all information that is collected within the eCRF, eg, dates when a subject visited the study site, records of study procedures, relevant medical history, or physical examinations, administration of Study Vaccine and Investigational Product or concomitant medications, any AEs experienced, and any other records as appropriate. These records constitute source data.

An eCRF will be provided by Seqirus (or delegate) for each subject enrolled into the study. The Investigator is responsible for ensuring accurate and proper completion of the eCRF in a timely manner so that it always reflects the latest observations on the subjects enrolled in the study. All entries on the eCRF must be backed up by source data.

All source data will be kept according to all applicable regulatory requirements.

The subject diaries will be completed by the subject's parent(s)/guardian(s) at home.

Immunogenicity and virological tests will be conducted by an external vendor laboratory. The test results from the vendor's database will be integrated into the study clinical database. The data integration process is described in the non-eCRF data integration document.

14.5.2 Data Quality Assurance

Data generated throughout the study will be monitored and the eCRFs checked against the subject source records, where available, for completeness and accuracy. Seqirus' study monitor (or delegate) will perform this function.

Following completion of eCRF pages and entry of the data into a database, the data will be checked electronically for consistency and plausibility. Queries will be generated for questionable data and clarification sought from the Investigator. These data queries must be resolved in a timely manner by the investigator (or delegate).

14.5.3 Record Retention

Files prepared by Seqirus (or delegate), containing all applicable documents for use at the study site, will be made available to the Investigator before the start of the study. All study documentation and materials maintained in the Investigator Study File must be kept in conformance with applicable national laws and regulations.

All study documentation and materials maintained in the Investigator Study File at the study site must be available for inspection by the Seqirus study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited or inspected by qualified delegates from Seqirus or a competent regulatory authority.

Following completion of the study, the Investigator is responsible for archiving the Investigator Study File, the subjects' records and the source data according to applicable regulatory requirements.

14.6 STUDY AND SITE CLOSURE

Seqirus reserves the right to prematurely discontinue or suspend the study either at a particular site or at all study sites at any time and for any reason. If such action is taken, the Seqirus Study Monitor (or delegate) will discuss this with the Investigator at each study site at that time and notify the investigators in writing. If the study is suspended or terminated for safety reasons, all investigators and the relevant regulatory agencies will be immediately notified of the action as well as the reason for it. The Investigator at each study site will advise the IRB overseeing the study at their site.

14.7 CLINICAL STUDY REPORT

A clinical study report will be written after the interim analysis and after the completion of the study. Seqirus will write the report.

Progress reports may be provided to the relevant regulatory bodies in accordance with their requirements.

14.8 USE OF DATA AND PUBLICATIONS

The rights and obligations of investigators and Seqirus concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Agreement for the study.

15 REFERENCES

Ambrose CS, Levin MJ. The rationale for quadrivalent influenza vaccines. *Hum Vaccin Immunother* 2012 Jan; 8(1):81-8.

Armstrong PK, Dowse GK, Effler PV, Carcione D, Blyth CC, Richmond PC, Geelhoed GC, Mascaro F, Scully M, Weeramanthri TS. Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine. *BMJ Open*. 2011 May 30;1(1):e000016.

Belshe, RB. The need for quadrivalent vaccine against seasonal influenza. *Vaccine* 2010 Sep 7; 28 Suppl 4:D45-53.

Blyth CC, Currie AJ, Wiertsema SP, Conway N, Kirkham LA, Fuery A, Mascaro F, Geelhoed GC, Richmond PC. Trivalent influenza vaccine and febrile adverse events in Australia, 2010: clinical features and potential mechanisms. *Vaccine*. 2011;29(32):5107-5113.

Brady RC, Hu W, Houchin VG, Eder FS, Jackson KC, Hartel GF, Sawlwin DC, Albano FR, Greenberg M. Randomized trial to compare the safety and immunogenicity of CSL Limited's 2009 trivalent inactivated influenza vaccine to an established vaccine in United States children. *Vaccine*. 2014 Oct 29;32(52):7141-7147.

Center for Biologics Evaluation and Research (CBER). Guidance for Industry: E2F Development Safety Update Report. Maryland (US): Food and Drug Administration, U.S. Department of Health and Human Services; 2011.

Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) – United States, 2013-2014. *MMWR* 2013; 62(RR-07):1-43.

Centers for Disease Control and Prevention. Update: recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding use of CSL seasonal influenza vaccine (Afluria) in the United States during 2010–11. *MMWR*. 2010;59:989-92.

Department of Health and Ageing Therapeutic Goods Administration. Investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination: status report as at 2 July 2010. [updated 24 Sept 2010; cited 16 January 2014]. Available from: <http://www.tga.gov.au/pdf/alerts-medicine-seasonal-flu-100702.pdf>.

Fiore AE, Shay DK, Broder K, Iskander JK et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR Recomm Rep* 2009 Jul 31;58(RR-8):1-52.

Monto AS. Epidemiology of influenza. *Vaccine*. 2008 Sep 12; 26 Suppl 4:D45-8.

Reed C, Melter MI, Finelli L, Fiore A. Public health impact of including two lineages of influenza B in a quadrivalent seasonal influenza vaccine. *Vaccine* 2012 Mar 2;30(11):1993-8.

Rockman S, Dyson A, Koernig S, Becher D, Ng M, Morelli AB, Barnden M, Tang ML, Pearse M, Maraskovsky E. Evaluation of the bioactivity of influenza vaccine strains in vitro suggests that the introduction of new strains in the 2010 Southern Hemisphere trivalent influenza vaccine is associated with adverse events. *Vaccine*. 2014 Jun 24;32(30):3861-8.

Rockman S, Becher D, Dyson A, Koernig S, Morelli AB, Barnden M, Camuglia S, Soupourmas P, Pearse M, Maraskovsky E. Role of viral RNA and lipid in the adverse events associated with the 2010 Southern Hemisphere trivalent influenza vaccine. *Vaccine*. 2014 Jun 24;32(30):3869-76.

Rota PA, Wallis TR, Harmon MW, Rota JS et al. Cocirculation of two distinct evolutionary lineages of influenza type B virus since 1983. *Virology* 1990 Mar; 175(1):59-68.

Rothberg MB, Haessler SD, Brown RB. Complications of viral influenza. *Am J Med* 2008 Apr;121(4):258-64.

Temte JL, Prunuske JP. Seasonal influenza in primary care settings: review for primary care physicians. *WMJ* 2010 Aug;109(4):193-200.